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ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION FOR THE STUDY OF

INTERNAL SECRETIONS

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ENDOCRINE STUDIES: XXXV. THE ASSOCIATION OF HEPATIC DYSFUNCTION WITH THYROID FAILURE*

ALLAN WINTER ROWE

Evans Memorial, Massachusetts Memorial Hospitals

BOSTON

In a paper on the thyroid (1), published in 1928, attention was drawn to the frequency with which thyroid failure was complicated by various types of hepatic dysfunction. In this earlier series, the representation of the dysfunctional and hyperfunctional forms of thyroid disorder was numerically inadequate to warrant any generalization relative to their inclusion; in the later studies, reported here in part, thyroid dysfunction of the transition type is so commonly associated as to be significant, although its incidence occurs less often than that of established functional failure. The present paper deals only with the group in which clear-cut failure was demonstrated.

That the thyroid occupies a unique position in respect to the liver is attested by the relative frequency of hepatic complication in a variety of other conditions. The results of a survey of a group of consecutive series of cases presenting conditions unassociated with the thyroid, together with a group showing thyroid failure, have been collected in tabular form.

TABLE I

RELATIVE INCIDENCE OF HEPATIC COMPLICATION

Condition—	*Total Cases*	*With Hepatic Complication*	
		Number	*%*
Thyroid Failure	664	149	22.44
"Non-Endocrine"	1840	336	18.26*
Pancreas	28	4	14.29*
Gonad	509	40	7.86*
"Pluriglandular"	36	2†	5.56
Pituitary	1546	50	3.23

*See text.
†Both castrates with thyroid failure.

Inspection of the table shows the thyroid group to be well in the lead. The next group marked "non-endocrine" is a collection of consecutive

*Read before the Sixteenth Annual Meeting of the Association for the Study of Internal Secretions, New Orleans, May 10, 1932.

cases presenting a wide scatter of conditions, none of which are associated with the ductless glands. The magnitude of the incidence of liver disorders is definitely misleading as in the latter part of this consecutive series are included a very considerable group of known liver cases, admitted as such, for study. In an earlier series of five hundred "non-endocrine" patients the hepatic factor was only 2.60 per cent, while in a more completely studied intermediate series of nearly fourteen hundred cases, the incidence of hepatic dysfunction was 5.81 per cent. These lower figures are far more characteristic than the higher, weighted value given in the table. Even with its non-representative magnitude, it falls short of the observed incidence in the thyroid group. In a like manner, three of the small series of diabetics listed here were of the "bronzed" type and were admitted selectively. They had all been referred for study as potential cases of Addison's disease; investigation established their true etiology. In the gonad group, 13 of the 40 positive subjects were castrates; the incidence of liver disorder in the functional cases was 5.30 per cent.

Finally, combining all of the series given in the table, with the exception of the thyroid group, it is evident that in nearly four thousand cases the incidence of hepatic disorder is at most 10.91 per cent—less than half that in the thyroid series—and this value is derived from data heavily overweighted, most significantly in the "non-endocrine" group.

Hepatic dysfunction produces a series of characteristic symptoms. Equally, it exercises a significant influence on many of the objective data, the measurement of which determines the functional status of the individual. Recognizing these facts, analysis has been made to ascertain how far these superimposed effects may mask the fairly clear-cut pictures of uncomplicated thyroid failure. In a way, this last term is perhaps unwarranted as thyroid failure, per se, is not usually encountered in an individual demonstrably free from any other significant departure from the physical normal. As the question will be considered later in the text, it may be passed for the moment.

A second objective of the study was to determine how far the combined influences of the thyroid failure and hepatic dysfunction might produce in the individual a clinical and laboratory picture suggestive of some other morbid state with an entirely different basic etiology. The significance of this aspect for diagnosis and complementary treatment is apparent.

The material for the study was drawn severally from a consecutive series of one hundred cases of demonstrated liver disorders of various types and a like series of established cases of thyroid failure with liver complication. In the case of the liver series, 94 gave definite evidence of hepatic involvement by the liver function test (McClure) (2) as well as numerous other objective indices in the history, physical and laboratory examinations. The data on the six cases not examined by the duodenal technique were as follows:

B-1271 was a seven-year-old child with a history of severe jaundice and a completely consistent laboratory picture.

B-1395 and B-1629 had both had cholecystectomies, while B-1585 and B-1786 gave positive Graham tests at the time of the intitial study and were operated upon before the liver function test could be performed.

Case B-1535 was a patient with cirrhosis of the liver with marked hepatic enlargement and severe jaundice. He was too ill to undergo intubation for the liver test and died shortly after the study. The diagnosis was confirmed at autopsy.

Characteristic laboratory findings were obtained with all of this group.

The evidence of hepatic complication in the thyroid group may be considered somewhat more in detail and the various data are collected in the following table. Both the total number giving a positive report and that selected as the primary evidence in the several categories are given.

TABLE II

EVIDENCES OF HEPATIC DYSFUNCTION

Datum	*Positive Report*	*Primary Evidence*
Liver Function	78	78
Graham Test	28	10
Cholecystectomy (earlier)	5	1
Surgical Examination	44	6
History	84*	5*
Total		100

*See text.

Nearly four-fifths of the entire series were able to take the duodenal tube, and the examination of the material thus obtained gave objective evidence of significantly depressed biliary activity. Of the remainder, positive Graham tests, surgical examinations demonstrating hepatic enlargement or gall bladder disease, and one case with a history of previous cholecystectomy, accounted for all but five. With these, the study of whom was incomplete for a variety of reasons, a characteristic history, coupled with completely supporting laboratory evidences, was felt to warrant their inclusion in the group.

Some interest may attach to the 16 cases giving entirely negative histories. Thirteen of these showed definite hepatic dysfunction by the examination of the duodenal contents, one, a positive Graham test, while the remaining two exhibited tenderness in the gall-bladder area on surgical examination which was interpreted by the surgeon as indicating local disease. Again, in every instance, the laboratory findings were consistent with liver involvement.

As hepatic dysfunction is the sole common feature of all of the cases under consideration and, further, as the positive examination of the duo-

denal contents constituted the primary evidence to support a liver diagnosis in 86 per cent of the complete group of cases, the actual results with this method of approach may be briefly considered.

TABLE II-a

LIVER FUNCTION (McCLURE)

Datum	*Positive Response* — *Thyroid-Liver*	*Liver*
Number of Cases	78	94
Color—		
Brown	15%	9%
Yellow Brown	18%	22%
Yellow	65%	65%
Green	1%	4%
Furfurol Index (below 80)	85%	88%
Cholesterol (below 30)	53%	55%
Pigment I (below 8.0)	87%	85%
Pigment II (below 7.0)	77%	82%

In the thyroid-liver group, 15 per cent, as against 9 per cent in the non-endocrine series, showed the brown color which is found in normal collections and the presence of which in cases of dysfunction usually is associated with mild states of depression. The other figures, in the main, show a rather striking concordance. Analysis of the relative frequency of positive response to the several tests applied would seem to indicate that the furfurol index is most sensitive to functional depression, with the two pigment groups at almost the same level. The cholesterol content seems to be the least affected, only about half of the cases showing depression below the established low normal limit of 30 mgm. There is a suggestion in this observation relative to cholesterosis and gall stone formation, discussion of which is not apposite to the present thesis. The magnitudes of the several reports of positive response indicate that the great majority of the patients presented hepatic dysfunctions ranging in degree from moderate to severe, a favorable experimental condition as it insures clear definition to the changes attributable to the liver status.

Earlier in the paper attention was drawn to the fact that the existence of one disease state or dysfunctional condition does not exclude other coexistent abnormality in the same individual. A review of the complete records of the cases composing the two series discloses certain rather striking facts. The prevalence of focal infections, either in the operative history or current examination, or both, challenges attention. The records are collected in Table III.

The cases reported under the caption of "examination" are corrected for those with a positive operative history which could, however, leave positive residua, as in the case of the tonsils. Further, the number showing positive physical evidences has been deleted of those who also gave positive x-ray evidence. In the main, there is a rough general parallelism in frequency of report though the liver group shows a definitely larger

TABLE III

FOCAL INFECTIONS, PAST AND PRESENT

	Operative History	*Examination Radiological*	*Physical*	*Total**
Sinuses				
Thyroid-Liver	9	17	5	31
Liver	8	12	11	31
Tonsils				
Thyroid-Liver	40	..	21	61
Liver	40	..	27	67
Teeth				
Thyroid-Liver	13	13	30	56
Liver	14	32	29	75
Gall Bladder				
Thyroid-Liver	5	27	17	49
Liver	11	27	21	59
Appendix				
Thyroid-Liver	24	17	3	44
Liver	30	13	9	52
Lungs				
Thyroid-Liver	..	26	..	26
Liver	..	31	..	31

*Corrected for duplication.

proportion with past or present dental disease and significantly higher figures for involvement of both the appendix and the gall bladder. Too sweeping a generalization should be avoided, but it seems warranted to note that in both series there is evidence of general background of infection, much of which is of many years' standing as indicated in the individual case history.

In addition to the rather impressive list of past or present infections, there is a variety of complicating conditions in both series which are of sufficent gravity or frequency of report to warrant notice. These are collected in the next table.

TABLE IV

SIGNIFICANT COMPLICATIONS

Condition	*Thyroid-Liver*	*Liver*
Arthritis	7	18
Syphilis	3	3
Allergy	4	9
Malignant Tumor	2	1
Intoxications, Chronic	0	4
Neural Disease	8	9
Cardiac Disease	12	15
Hypertension	9	8
Genito-Urinary Disease	5	15
Nephrosis	5	12
Gastro-Intestinal Disease	13	15
Pelvic Disease	9	8
Neuroses	7	12
Psychoneuroses	4	9
Psychoses	4	1

Incipient or mild conditions, such as arthritis, which are capable of exhibiting a significant range of gradations, are not reported in those groups. While the figures are informative, individual items call for more

extended notice. The four cases of chronic intoxication were severally "ergoapiol," lead, carbon tetrachloride, and Epsom salts. In the last instance, a long-standing addiction had seemingly influenced subversively the osmotic relationships in the tissues. The neural group included postmeningeal and encephalitic cases, those with head trauma, and one case each of multiple sclerosis and an indeterminate cord lesion of traumatic origin. The patients with genito-urinary disease comprised those with pyelitis, cystitis, prostatic enlargement with the usual sequelae, and marked nephroptosis with acute ureteral angulations. Patients presenting only the residua of child-bearing were excluded from the "pelvic" group which included several fibromata and an unrecognized pregnancy. The psychoneurotic groups are included both for the sake of completeness and because their presence in a few of the patients prevented the performance of certain important tests.

To summarize briefly, 56 of the thyroid-liver cases, in addition to their numerous focal infections, presented 93 significant departures from the normal, an average of 1.66 per person; in the liver group, 82 individuals demonstrated 139 additional complications, an average of 1.69 per person, or practically the same as the thyroid series. In other words, both series show a marked incidence of focal infective processes above the normal prediction in an unselected series of individuals, and concurrently, the presence in the majority of each group of a wide variety of definite morbid conditions, some of which at least are of a very real gravity. Further, the individuals in the combined thyroid-liver group seem to be somewhat less burdened with significant complications than their fellows in the simple liver series. The majority of the differences, however, are not great.

Turning now to certain of the categories of data presented by the composing cases in the two series, the sex and age relations are collected in Table V.

TABLE V

	Thyroid-Liver	*Liver*
A. Sex		
Male	32%	23%
Female	68%	77%
B. Age		
Less than 21	10%	8%
21-30	22%	25%
31-40	25%	25%
41-50	25%	26%
51-60	13%	9%
Over 60	5%	7%
Average Age	37.7 Yrs.	38.1 Yrs.
Extreme Ages	13-78 Yrs.	7-71 Yrs.

The females outnumber the males two to one in the composite group and nearly three to one in the simple liver series. In a series of 350 thyroid cases reported elsewhere (3), the male representation was 29 per

cent, or substantially the figure here recorded. From the same source, our analysis of one thousand "non-endocrine" cases of all kinds shows the male percentage to be 39. The discrepancy with the present figures seems to indicate a greater susceptibility of the female to hepatic involvement, a finding in harmony with the numerous records widely reported in the literature.

The age scatter of the two groups is substantially the same. Referring to the compilations noted above (3), the thyroid series shows 22 per cent of the cases examined before the twenty-first year with correspondingly lower values for the third, fourth, and fifth decades, and approximately equal incidence thereafter. The "non-endocrine" series parallels the course of the thyroid. A possible interpretation would be that the hepatic element is frequently a secondary manifestation to a condition developing earlier in life; this formulation could then carry with it the corollary that the hepatic overload tends to curtail the years of life. The acceptance of this explanation would demand a much larger volume of supporting evidence than the present paper contains. The important point of the current analysis is the consistency between the data of the two series.

The family hisory of many patients has but dubious objective value. Ignorance and misinformation, on the one hand, coupled with an intentional suppression of those conditions stigmatized in the common reaction, frequently render the patient's report of less than no value for any statistical approach. With just recognition of this limitation, the values obtained from the records are given in Table VI.

TABLE VI

FAMILY HISTORY

	Thyroid-Liver	*Liver*
Cancer	31%	25%
Cardiovascular Disease	31%	42%
Tuberculosis	27%	21%
Diabetes	10%	10%
Goiter	13%	6%
Mental Disorder	7%	6%
Syphilis	(2%)	(1%)

The incidence of cancer in the thyroid-liver group is distinctly higher than in similar compilations, a report from a series of several hundred thyroid cases being but 19 per cent. The patients with thyroid failure report goiter twice as frequently in their family history as do those in the simple liver group. The report on familial syphilis is included to emphasize the criticism offered in the opening sentence. The other figures offer nothing distinctive.

The symptoms which form so large a part of the medical history can be divided into two groups. The first of these, the chief complaint, or usually, complaints, constitutes one of the most subjective of evidences in the entire record. The emphasis is that of the patient, and a variety of

factors unassociated with the underlying condition may play important roles in determining its content. A classic example is the woman whose chief complaint is of overweight and who is actually 10 to 15 per cent below the predicted normal.

More informative and authoritative is the total report of a given symptom compiled from the entire case record. Here the element of emphasis is omitted and the factors conducing to erroneous report much less in evidence. In the next table have been collected the data deriving from the two series of symptoms, which may properly be regarded as suggesting, although not defining, an hepatic factor. In order to control the endocrine element in the thyroid-liver group, data from the review of a consecutive series of 100 patients with thyroid failure and without a liver complication have been entered in the column marked "Thyroid."

TABLE VII

SUGGESTIVE SYMPTOMS

	Chief Complaint		*Total Report*		
Symptom	*Thyroid-Liver*	*Liver*	*Thyroid**	*Thyroid-Liver*	*Liver*
Headache	16	22	55	76	76
Vertigo	13	6	32	57	59
Abdominal Pain	20	34	16	39	43
Fatigue	40	34	61	84	79
Disturbances—					
I. Gastro-Intestinal*	22	28	25	84	91
(a) Nausea, Vomiting.	8	4	13	48	50
(b) Flatulency	5	4	36	57	67
(c) Constipation	3	3	44	66	58
(d) Jaundice	2	3	3*	27	28
II. Menstrual†	12%	0	59%	52%	29%
(a) Irregular	6%	0	42%	31%	14%
(b) Abnormal Periods	0	0	52%	34%	23%
(c) Dysmenorrhoea	2%	0	31%	35%	25%
III. Visual	3	7	..	35	37

*See text.
†Percentages based on matured females.

Headache is a common symptom of thyroid failure but is recorded with greater frequency in the groups with a liver complication. Vertigo seemingly is more an expression of the liver influence, though perhaps not quite as strikingly as the report of abdominal pain. They are all fatigable, but the patients with the double burden of endocrine failure and liver derangement show the highest incidence of report for this symptom.

A general report of gastrointestinal disturbances is patently traceable to the liver influence, and this conclusion finds confirmation in the record of individual symptoms. Even the simple thyroid case, with whom constipation is a usual report, falls short of the liver group, which in turn is below that of the combined condition. The three subjects in the thyroid group reporting jaundice, gave records in their histories of this condition in earlier years. A possible hepatic residuum might be deduced for them,

but the remaining study contained no significantly supporting evidence. The thyroid influence, in turn, dominates the menstrual history. The incidence of abnormality is greater in the simple than in the complicated thyroid group, a record contrary to anticipation. An explanation that seems reasonable is that in the simple group the thyroid aberration is of longer duration and thus has produced more disturbance in a somewhat delicately balanced function which it influences.

Briefly summarized, there is a general similarity between the incidence of the general symptoms in the two major groups; in addition, the liver dominates the gastrointestinal, the thyroid, the menstrual picture.

In an earlier paper (4) I have shown the seemingly depressing influence of endocrine disorders on human fertility. A like analysis has been made of the two groups under discussion to ascertain if the trends there disclosed are repeated. The pertinent data are given in Table VIII.

TABLE VIII

MARITAL ANALYSIS

Datum	*Thyroid-Liver*	*Liver*
I		
Total Number	100	100
"Marriageable"	87	93
Married	64	61
Per Cent	74	66
Average Duration	16 Yrs.	18 Yrs.
II		
Total Infertile	20	23
Married less than 3 years	3	2
Contraception	1	1
Abortion	0	2
Net Infertile	16	18
Per Cent	27	32
III		
Total Conceptions	211	162
Abortions	6	17
Net Conceptions	205	145
Children	159	123
Productive Conceptions	78%	85%

The term "marriageable" given in Section I is applied to males twenty-six years of age and over and to females of twenty-one or more. These limits are arbitrary, as would be any others adopted. They are derived from an extensive study of the marrying age of a large group of representative unions, and the values assigned are felt to be reasonably representative of this community.

In the present instance, three-fourths of the eligible thyroid-liver patients and two-thirds of the simple liver group have married. The thyroid figures from the analysis cited above (4) was 67 per cent, or that of the present liver series. Evidently the double burden offers no impedance to a desire for marriage, a point which will be touched on later.

In Section II another arbitrary limit is established—with the same warrant as obtained with the first. Again, survey of community data

suggests the unwisdom of designating a union as infertile until at least three years of exposure have elapsed. Like any other assumed limit, it presumably operates uniformly throughout the groups concerned. Applying the convention uniformly, it is evident that the simple liver group is slightly less fertile than is the combined series, although the average duration of married life is somewhat greater. The same datum from the paper cited shows a net infertility in a large series of thyroid cases to be 31+ per cent, while in the special series of 100 cases, data from which were given in Table VIII, the figure is 32 per cent. Here again, the thyroid influence, reinforced by that of disordered liver function, is seemingly less inhibiting to fertility than either the liver or endocrine influence alone. This is naturally contrary to anticipation and requires interpretation. One other point may be touched on in this connection. Of the 16 thyroid-liver cases with infertile unions, nine of the patients had never conceived, while the remainder had miscarried after impregnation. In the simple liver group, of 18 infertile marriages, 12 subjects had never conceived, and six had miscarried. In the uncomplicated thyroid group used for control in Table VII, 20 matings were infertile of the 63 unions recorded. Of the 20 infertile subjects, 18 had never conceived and only two infertility reports had resulted from miscarriage. Incidentally, one of these patients had miscarried eight times in 16 years of married life. There was no obtainable venereal history, and serological tests were negative.

Turning to Section III of the table, the thyroid-liver group shows a somewhat smaller percentage yielding viable children of the conceptions recorded than is the case with the liver group. The figure 78 per cent is that of the control thyroid group noted above (110 children in 141 conceptions), while it is 77 per cent in the larger thyroid series already cited (4).

The thyroid influence here is consistent and, at first sight, uniform. Further analysis shows a relationship more in harmony with the preceding data. The several pertinent figures are given in Table VIII-a.

TABLE VIII-a

CHILDREN FROM PRODUCTIVE MARRIAGES

Group	*Fertile Unions*	*Viable Children*	
		Total	*Per Mating*
Thyroid-Liver	44	159	3.6
Liver	38	123	3.2
Thyroid (Control)	43	110	2.6
Thyroid (4)	120	246	2.1

If one takes the actual fertile unions and the average number of children produced by each, it is evident that the doubly burdened thyroid-liver group has the highest productivity, while the depressing influence of thyroid failure alone is clearly evidenced. Again, the figures suggest a late onset of the thyroid factor in the combined group, an onset that post-dates marriage and the establishment of a significant degree of fertility.

Emphasis has been laid upon the marital analysis as it is one of the considerations most strongly suggesting—although not defining—a progressive sequence in the thyroid-liver relationship. Others will be reviewed in the body of the text.

We may next turn to the consideration of certain of the laboratory data as it is peculiarly in this group of evidences that the differential diagnostic aspects find expression. Simple thyroid failure produces characteristic changes in certain levels of function and physical features of the individual; equally, disordered liver function exercises its influence along similar or identical lines. Where the influences are alike in directional trend, one would, a priori, anticipate a reinforcement of the one by the other. Opposite influences, equally, would tend to nullify each other and the measured end result become an algebraic summation of forces not necessarily equal. Yet other magnitudes may come to measurement, which are influenced by one but not the other. How far these inferences are warranted will be considered in the subsequent discussion.

The first group of evidences to present for consideration are two easily secured biometric observations, namely, weight and lung volume.

TABLE IX

BIOMETRIC RELATIONS

	Thyroid-Liver	*Liver*
Weight		
Above Normal Range (+15%)	39	18
Average Amount	+39%	+33%
Normal Range (—10% to +15%)	36	55
Below Normal Range (—10%)	25	27
Average Amount	—20%	—20%
Lung Volume		
Above Prediction	15	11
Average Amount	+7%	+7%
Within Normal Range (—15%)	27	22
Below Normal Range	58	67
Average Amount	—29%	—18%
Sitting Height Index	0.531	0.532

Comparative results with an accepted standard which absorbs such variables as sex and age are for certain purposes more meaningful than the absolute data from which they are derived. The weight comparisons are based upon Dreyer's (5) standards referred to sitting height, and those of lung volume are the average of the Dreyer prediction ("A" for men and "B" for women) and the mean of the two West (6) standards referred severally to height and area.

More than twice as many of the thyroid-liver series are overweight than are the components of the liver group, and the degree of the obesity is somewhat greater. One-third of the first and one-half of the second series are within the normal range. The underweight fractions show a definite parity. The usual tendency of thyroid failure to produce overweight is clearly reflected in these figures. Some further support is found in the underweight group as the writer has described an amyxedemic

type of thyroid failure (1) whose physical habitude is underweight—not overweight—and who gains with the normalizing of glandular function through opotherapy.

The depressing effect on lung volume is more manifest in the present series in the amount of the depression than in the number showing it, as more of the liver series give values that are below prediction than are those in the combined group. The relative degrees are consonant with the well-known thyroid influence. The chronology of onset of the thyroid failure as compared with that of hepatic dysfunction might be adduced to explain the significant number showing normal levels.

The somewhat high values for the sitting height index no more than reflect the predominance of females in both series.

Selecting only the more significant urine findings, the data are collected in the next table.

TABLE X

URINE MEASUREMENTS

Datum	*Thyroid-Liver*	*Liver*
Albuminuria	48	72
Glycosuria	9	18
Total Nitrogen (Av.)	8.67 gms.	7.20 gms.
Ammonia Nitrogen	3.8%	4.3%
Residual Nitrogen	8.5%	8.3%
Per Cent Residual Above Normal	42	36

While practically half of the thyroid-liver group show small amounts of albumin in the urine—a value materially in excess of that (20 per cent) elsewhere recorded (7)—three in every four of the simple liver group give this evidence of renal derangement. Reference to an earlier table (IV) will show a definitely larger incidence of genito-urinary disorders in the latter group. Thyroid failure produces what the writer has designated as a "pseudo-nephritis," a condition manifesting itself in both the blood and urine chemistry with indications of a lowered renal permeability; this tends to disappear when the gland is brought to a functional normality. In liver disorder toxaemia is common, the degree of the toxaemia reflecting in some measure that of the hepatic involvement. In the present instance, the uncomplicated liver cases would seem to present a more severe degree of hepatic impairment, a deduction supported by the better protein exchange in the thyroid-liver group. Neither series gives evidence of an acidotic tendency, and the slightly higher values for the amount of residual nitrogen and the more frequent occurrence of values above normal may well be attributed to the added thyroid influence.

In a similar manner, the more frequent report of glycosuria in the simple liver group presumably reflects the opposing influence of thyroid failure in which the utilization power for carbohydrate is increased within modest limits.

The significant blood reports are given in Table XI.

TABLE XI

BLOOD MEASUREMENTS

Chemistry	*Thyroid-Liver*	*Liver*
Non-Protein Nitrogen	31.5 mgm.	30.6 mgm.
Urea Nitrogen	15.5 mgm.	15.0 mgm.
Uric Acid	3.5 mgm.	3.3 mgm.
Residual Nitrogen	14.2 mgm.	13.9 mgm.
Sugar	92 mgm.	92 mgm.
Morphology		
Haemoglobin	83.7%	81.2%
Erythrocytes (10^6)	4.76	4.61
Color Index	0.88	0.88
Leucocytes (10^3)	7.75	8.29
Lymphocytes	36	33
Eosinophiles	2.5	2.4
Per Cent with 3% or more	41	37

The nitrogenous constituents in general show nothing remarkable with the exception of the uric acid which is high in both groups. This is seemingly due to a liver influence, as it appears in both series, and a representative figure for a group of thyroid cases without liver complication is 2.7 mgm., definitely below the upper normal limit of 3.0 mgm. The present figures give no evidence in their entirety of that "pseudo-nephritis" which, as already noted, is a frequent feature of long-standing thyroid failure. So far, again, as these figures can be meaningful, they accord with the assumption that the thyroid element is of a secondary and sequential nature.

The haemoglobin and erythrocyte averages are suggestive of a mild secondary anaemia, and many of the individual records in each series show this condition in well-marked degree. The slightly higher leucocyte average for the simple liver group may be due to the somewhat larger number of patients with active cholecystitis. The slight lymphocytosis in the thyroid-liver series is in harmony with the tendency toward somewhat increased lymphocyte fractions frequently associated with thyroid failure as well, of course, as a wide variety of other conditions.

The eosinophile values are high for thyroid failure and the incidence of individual high values, definitely above the usual report. In an earlier series, these values for thyroid failure were respectively less than 2 per cent and 25 per cent. A liver influence would seem to be traceable here. With the liver apparently playing the more significant role in the determination of the formula of the blood morphology, it is to be anticipated that the two series will show values that are mutually in agreement.

With the consideration of the respiratory metabolism one encounters evidence of a principal influence on function level exercised by the thyroid.

While in all of the thyroid cases findings are below the low normal boundary and present an average 27 per cent under prediction, in the liver cases there is but a minor associated depression of the respiratory exchange and that further in but one-fourth of the total series. While not recorded in the table, it may be added that the other three-quarters all give values

TABLE XII

RESPIRATORY METABOLISM

Datum	*Thyroid-Liver*	*Liver*
Basal Metabolic Rate		
Below —9%	100	27*
Average Deviation of Low Group	—27%	—13%
Lowest Reading	—44%	—18%
Blood Pressure		
Group A	(91) 108/64	(92) 110/64
Group B	(9) 172/100	(8) 186/104
Pulse Rate	60	72
Respiration Rate	12	15
Temperature	97.9	98.1
Alveolar CO_2	43	42

*Inadequate protein utilization and malnutrition.

within the conventional normal range. The average deviation of the low liver group of —13 per cent is hardly significantly below the conventional inferior normal limit, and the case showing the extreme deviation falls notably short of the average value for the group with thyroid failure. Further, analysis of the individual records of the low simple liver group shows them to be derived, scarcely without exception, from individuals giving concrete evidence of malnutrition and inadequate protein utilization. As is generally recognized, these conditions depress the respiratory exchange significantly, and in the present instance this fact serves to explain the individual departure from a normal oxygen requirement. The endocrine influence is unmistakable in the levels for this datum in the two series.

The blood pressure figures are very interesting. Thyroid failure produces initially an established hypotension, but in long-continued cases, with changes in the vascularity of the arterial wall, an augmenting influence is developed which raises the blood pressure to normal or even to hypertensive levels. In the thyroid-liver group are nine patients with established hypertension. It will be noted further, that the pulse pressure in the hypotensive group is relatively somewhat high. Despite the fact that the phlegmatic and dull individual is the classic prototype of thyroid failure, many of them have a definite nervous instability more or less masked by their apathetic behavior. The thin amyxedemic patient is usually frankly nervous, and the different mental habitus of this type conduces to its clear-cut expression. In my opinion, the systolic average here is probably higher than the basal level, but as the picture is characteristic of the condition, it is representative as for the same reason are the inaccurate observed basal rates so frequently recorded in cases of ovarian failure. An average for a series of thyroid cases earlier reported is 112/72 mm.

Another element enters into the consideration of the blood pressures of the simple hepatic group. The complete agreement with the data from the thyroid-liver series is, in my opinion, one more of those instances where a common end result may be produced by a variety of presumably unrelated causes. Lowered liver function is usually associated with hypoten-

sion, either tendential or established. In this group, too, there is a nervous element and the somewhat high pulse pressure suggests that the systolic average for the simple liver group may be somewhat in excess of the true level; as in the thyroid series, nearly one-tenth show a very definite degree of hypertension. In a series of studies by the author and his associates (unpublished data) on the physical background of what is called "essential hypertension," it has been remarked that one definite group among the several falling under the major caption have definitely deranged hepatic function. A second and independent illustration is found in those toxaemias of pregnancy in which transitory hypertension is a feature and liver derangement a demonstrated factor (8). It seems probable that the usual effect of lowered liver function is to conduce to hypotensive levels of blood pressure. This could be conceived to be operative as a superimposed effect in the thyroid series since the levels here recorded are slightly below those already quoted from a control series of cases of thyroid failure. The two hypertensive groups, showing a misleading parity in numbers and amount, possibly arise from two different mechanisms, neither of which is fully understood at the present time. Phrased in another way, the hypertension of the thyroid group may derive from the endocrine influence and would be associated with decreased vascularity and so record a permanent change. That in the simple liver group, equally, may be of the same origin as the essential hypertension with liver complication or that associated with toxic pregnancy and is, initially at least, of a temporary character. Finally, that this latter form, persisting in long-standing cases of hepatic dysfunction, may, through secondary changes, ultimately become a permanent condition, should be freely conceded.

The depressions of pulse rate, respiration rate, and temperature, in the combined series are seemingly to be attributed to the thyroid influence. The complementary figures from a control series of thyroid failures are, respectively, 58, 15 and 97.9 degrees. The first and last, at least, are in excellent accord with the averages of the thyroid-liver series. The carbon dioxide tensions are normal and support the conclusion drawn from the urine ammonia that acidosis is not a feature of these cases in spite of the malnutrition that many of them exhibit. In addition, the urines were free from acetone and its precursors.

The carbohydrate metabolism depends on a series of interrelated mechanisms and functions, some of which at least are influenced by both of the major factors under consideration. Thyroid failure raises the utilization limit for galactose in approximately one case in three, the amount being of the modest proportions of from 33 to 50 per cent (1). Likewise, hepatic dysfunction influences galactose utilization, but usually in the opposite direction from thyroid failure and to a very much greater degree. In a series of 134 established liver cases (9), 108 or 81 per cent, showed a depression of the galactose tolerance, the average amount being —52 per cent. Eighteen had a normal tolerance and eight, or 6 per cent, a level

definitely superior to normal prediction, the average being +52 per cent. The implications of these latter results cannot be discussed here; the facts only are recorded.

In reporting the results of the galactose studies on this series, one complication calls for explanatory comment. The level of tolerance for normal women past the climacteric is not as sharply defined as for the other stadia of existence. Approximately one in three maintains the normal level of the sexually capable adult woman, namely 40 gms., while the other two sink to 30 gms. Thus it follows in testing women after the menopause a response at 40 gms. may mean a normal level or an increase of 33 per cent, while a level at 30 gms. can be interpreted either as a normal response or a tolerance depression of 25 per cent. To resolve the matter for this presentation and permit record without stultifying elaboration, deviations have been calculated from both bases and the average adopted. This operates equally in the two series as the number of post-menopausal females is substantially the same in both groups, i.e., 18 and 15. The detailed data are given in Table XIII.

TABLE XIII

GALACTOSE TOLERANCE

Datum	*Thyroid-Liver*	*Liver*
Above Normal, Number	3	2
Average Amount	+53%	+25%
Normal, Number	21	7
Below Normal		
To —33%, Number	25	20
Average Amount	—28%	—25%
—34% to —67%, Number	35	43
Average Amount	—54%	—54%
Over —67%, Number	16	28
Average Amount	—76%	—74%
Total Number	76	91
Grand Average Amount	—50%	—65%

Three of the endocrine and two of the simple liver cases show an augmented tolerance. In the second instance, this is clearly due to the occasional anomaly shown by liver cases and noted above. In the endocrine group it could be the effect either of the liver anomaly or of a thyroid influence operating effectively against the depressing liver effect. Inasmuch, however, as the uncomplicated thyroid failure of marked severity raises the tolerance only 50 per cent, it seems probable that all five of these cases express a primary liver influence. With the normal group, those in the endocrine series are three times as numerous as in the companion group. As the liver ordinarily lowers tolerance (v. s.), the probability exists that the majority at least of the normal cases in the endocrine series represent an algebraic summation of two opposing forces, fortuitously, in these individual cases, of equal strength.

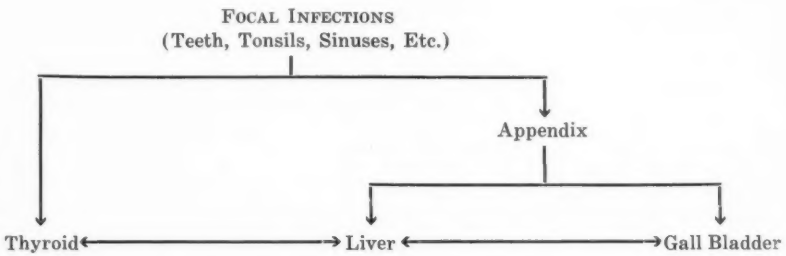
Turning finally to the two larger sections in which depressed tolerance prevails, the liver factor is obviously paramount and the opposing

thyroid influence serves only to mitigate the degree of the depression. The relative figures in the several sub-groups leave little doubt as to the correctness of this interpretation.

There are yet a number of other significant observations made in these series; it seems best to present them in subsequent papers. The material embodied in this paper can be briefly analyzed.

DISCUSSION

Many points have already been noted in the brief commentary on each group of data. A selective association of functional derangements of the thyroid and liver would seem to be established. If the other groups used for purposes of comparison were taken non-selectively, the incidence of liver dysfunction would be certainly four times as great in the thyroid group as in the combination of all of the others. Even with the heavily overweighted figures of Table I, the thyroid cases are relatively twice as numerous as the remainder of the combined groups. Just what may be the mechanism of this association is not established. Extensive and time-consuming investigations must be undertaken and completed before any sequence can be regarded as even reasonably established. As a suggestion, however, and one the lack of factual warrant for which the author is acutely conscious, the following schema may be offered for consideration:



No one step in the above may be regarded as established, but the data of the studies of the past twenty years offer some support to such a formulation, for one group of cases. It should be stressed that there is no inevitability to the coincident appearance of the three terminal conditions. A wealth of proven and tested evidence exists to deny any such generalization. True, evidence of liver dysfunction is usually found in the gall bladder case. The converse certainly is not true; the endocrine element may and usually does exist alone (see Table I), while only a small percentage of established liver cases demonstrate the endocrine complement. As stated above, the underlying mechanisms are patently obscure; equally, the present study demonstrates some degree of selective association between the two major components.

In considering the principal symptoms, those of headache, vertigo, and fatigue are characteristic of each component, and in the thyroid-liver group reach levels of frequency that implies a superimposition of one influence upon the other. Equally, the series of abnormalities associated with the gastro-intestinal tract indicate a primary liver agency, while, on the other hand, the menstrual irregularities derive initially from the influence of disturbed endocrine function. In this group of evidences, we have expression of independent activities of the two agencies and a reinforcement of one by the other. In the results of study of the carbohydrate metabolism are exemplified the algebraic summation of opposing forces. The specific thyroid effect on the respiratory metabolism offers a valuable differential point where the study is sufficiently complete to prevent its misinterpretation. This point leads to the consideration of the second major feature of the study, namely, the synthesis of a diagnostic picture characteristic of one condition from the combination of two other states unrelated to it.

The commonest type of pituitary disorder is that dysfunction in which the anterior lobe is underactive and the posterior lobe overactive. Further, the function picture of this condition, as mirrored in the laboratory tests and in some measure, the clinical findings, is definitely suggestive of functional ovarian failure. While it is true that there are a number of points of difference which, in the well-defined case, permit of a just discrimination, many cases present in which enough of these differential evidences are lacking to leave the final diagnosis a matter of probability rather than certainty.

Fatigability is a cardinal symptom of all of the endocrinopathies as well as of a number of disease conditions unassociated with the ductless glandular system. A tendency to undue fatigue or even asthenia turns the mind to an endocrine background as one of the several major causes.

Headache is another common report relatively more frequently associated with pituitary or ovarian disorders than with those of the thyroid. Visual disturbances of various types appear frequently with all of these conditions, with the thyroid midway between the ovary at the high extreme, and the pituitary at the low, when cases with tumor growth are excluded.

An endocrinopathy is probably the most frequently encountered origin of menstrual irregularities, and a positive report turns the attention at once to an investigation of the patient's endocrine status.

Aberrations of weight, particularly on the side of obesity, suggest possible endocrine causation, the relative frequency being, in order: pituitary, thyroid, and gonad.

In other words, the report of the several evidences just noted incline toward a potential endocrine background, even though they fail both to suggest a given endocrinopathy or even positively to define an endocrine condition.

Turning to the more sharply delimited laboratory evidences, a number of significant parallelisms are to be found. The liver cases tend to exhibit a normal urine volume, while pituitary urines are customarily normal or increased in amount. As there is some reason to believe that in many of the series, at least, the thyroid component was secondary and sequential to the hepatic condition, the depression of the urine output characteristic of thyroid failure had not been established. A positive response to Ehrlich's reagent is found in pituitary and liver cases, although, as has been pointed out previously, there is no valid reason to believe that it identifies the presence of the same compound in both. Primary anaemia likewise gives a positive response. Glycosuria is frequently found in liver and pituitary dysfunctions; rarely, if at all, in established uncomplicated thyroid failure.

High blood uric acid characterizes the liver and pituitary conditions but not the thyroid; here again the "pseudo-nephritis" of the latter is seemingly one of the later manifestations of an established condition. Slight eosinophilia is of frequent report in both pituitary and liver dysfunction; my own studies have failed to confirm its common presence in simple thyroid failure as has been reported by others.

On the other hand, depression of the basal metabolism is primarily an endocrine attribute and is manifested by the liver case only when serious malnutrition exists, and then in definitely lesser degree than with the endocrine failures. Liver dysfunction will depress the galactose tolerance to the same marked degree as will overactivity of the posterior lobe, while the effect of thyroid failure, when manifest at all, is to engender a slight upward trend.

Many other points could be adduced to define the thesis, but enough has certainly been said to warrant the conclusion that a combination of hepatic dysfunction with thyroid failure of moderate proportions can simulate both in clinical and in laboratory observations and tests, features that could readily be interpreted as defining a pituitary dysfunction of the usual lobar formula, or remotely a functional ovarian failure. The prejudicial effect of this error—or its converse—on subsequent treatment is too evident to need elaboration. The test of liver function, supplemented where necessary by a radiologic study using the Graham or similar technique, constitutes the crucial evidence for precise differentiation.

The protocols of a few illustrative cases are added.

Case S-3480. Amenorrhoea. The patient was a girl of 17 years complaining of an amenorrhoea of eight months' duration. She had matured at 15 and up to the time of abrupt cessation had flowed regularly at 35-day intervals, the periods lasting four to five days, with daily use of two to three napkins. During the preceding year she had lost some twenty pounds in weight but had dieted during the period to secure this result. Her history showed a remote family background of diabetes; she had been delivered by a Caesarian operation; the usual minor ailments and two attacks of scarlet fever were recorded. The remaining history as given was completely irrelevant. The physical examination showed a somewhat low blood pressure but was otherwise consistently normal.

The urine was normal in all respects, the nitrogen output at a low maintenance level. The blood pictures were:

Chemistry		*Morphology*	
Non-Protein Nitrogen	27	Haemoglobin	84
Urea Nitrogen	13	Erythrocytes (10^6)	4.37
Uric Acid	4.3	Color Index	0.96
Creatinin	1.3	Leucocytes (10^3)	4.20
Sugar	83	Lymphocytes	51%
		Eosinophiles	4%

She was within one per cent of her predicted weight with a sitting height index of 0.512; in other words, slightly underweight. The lung volume was normal. Her first basal rate was 19 per cent below prediction; the second —25 per cent with blood pressure of 92/58, pulse 50, and respiration 8. The galactose tolerance was 50 per cent below prediction, the cardiogram normal. The eyes showed yellowish discs, with pulsating arteries and increased tortuosity of the vessels. The fields were normal as were the other eye measurments. Pelvic findings were normal. A radiographic study of the heart showed a slight generalized enlargement, the contour suggesting the so-called "myxedema" type.

The history, the generally normal physical findings, low sitting height index, normal urine, 'phthalein and alveolar carbon dioxide, together with the lymphocytosis, eosinophilia, high blood uric acid, lowered sugar tolerance, and moderately low basal rate, among other evidences, were all consistent with pituitary dysfunction which so frequently is associated with the condition named as the chief complaint. The case was diagnosed as of either pituitary dysfunction or thyroid failure with hepatic complication. The liver test was requested to resolve the question.

One hundred cc. of light yellow material were secured which gave the following values:

Datum	*Low Normal*	*Observed*
Furfurol Index	80	24
Cholesterol	30	18
Alcohol Insol. Pigment (I)	8	trace
Alcohol Sol. Pigment (II)	7	2.6

indicating a marked hepatic dysfunction which would account for those recorded departures from the normal not traceable to thyroid failure.

Case S-2720. Arthritis. This patient was a woman of 31 referred for a persistent and somewhat extensive polyarthritis which seemingly was due to an attack of rheumatic fever at the age of 24. In her own report she stated that the year before her visit she became sleepless, nervously unstable, fatigable, and suffered from palpitation. A metabolism test was found to be high, and she had been treated with some success for overactivity of the thyroid. This report was probably not consciously disingenuous, but the actual facts were as follows: She had been somewhat overweight (+27 per cent with the normal sitting height index of 0.524) and had been given thyroid substance to reduce her weight. This was apparently followed to the point of intoxication with a loss of some fifteen pounds. Her thyroid corrective treatment was for a thyrotoxicosis of medicinal origin. Her remaining history showed familial records of diabetes and goiter; she had borne one child uneventfully in four years of marriage; there was the usual record of minor ailments, and a tonsillectomy. She complained of severe headache, vertigo, palpitation, dyspnoea, some praecordial pain, edema of the feet, and some residua of her earlier thyroid intoxication. The menstrual history was normal in every way. Her examination showed some increase in tactile and vocal fremitus, but was otherwise not suggestive. There was no edema. The urine was somewhat scanty, elimination rather low, the protein exchange somewhat low, and a minute trace of albumin was reported. The blood analysis showed a high uric acid, the "morphology" a slight eosinophilia. She was still 15 per cent above her predicted weight, and the lung volume was 6 per cent above prediction, an unusual finding for a true thyroid case. The basal rate was —13 per cent (Harris-Benedict —10 per cent; Aub-duBois —15 per cent) with normal temperature, pulse and respiration rate, and a blood pressure of 98/58. The galactose tolerance was 50 per cent below normal prediction. The neurological examination was negative, the cardiogram normal except for axis deviation; this latter suggestion was denied by a radiographic

study of the heart which showed no enlargement. Other radiograms showed normal lungs, skull and sella; the right frontal and maxillary sinuses showed thickened mucous membrane with slight osteitic reaction. A radiologic study of the gastro-intestinal tract showed a diseased appendix; the modified Graham (10) study, a chronic cholecystitis; stones were not certainly demonstrated.

This case is informative in two ways. In the first place, there is a polyarthritis with present or past disease demonstrated in (a) sinuses, (b) appendix, (c) gall bladder. Second, there is no demonstrable endocrine element other than the transitory intoxication resulting from an attempted reduction by thyroid medication of an obesity that was certainly not of thyroid origin.

The features suggesting pituitary dysfunction which derive from the liver condition are noted in the protocol.

Numerous other case records might be added to illustrate other points; these will be dealt with, however, in subsequent communications.

The possibility of hepatic dysfunction with its influence on certain vital function levels in patients with a normal gastro-intestinal history should be borne in mind. Further, liver disorders may complicate other disease states and functional derangements and thus produce both symptoms and objective measurements not suggestive of the primary condition. A frequent association, for whatever cause, between thyroid failure and hepatic dysfunction would seem to be established. The possibility of interpretation of this combination in terms of pituitary dysfunction has been discussed.

SUMMARY

In an earlier report the author described an apparent association between thyroid failure and hepatic dysfunction. The present paper analyzes a consecutive series of one hundred cases diagnosed as presenting both conditions, compared and contrasted with a like group showing the liver condition but without glandular involvement. For certain of the points under consideration data from a third series of cases diagnosed as of uncomplicated thyroid failure is included.

The incidence of hepatic complication was found to be far more frequent with thyroid disease than with any other endocrinopathy. The clinical picture appears to be a synthesis by the two agencies which in some instances can be resolved into the component parts. For example, the gastrointestinal features can be traced to the liver influence, the menstrual irregularity to the thyroid.

In similar manner, the objective measures of vital function level such as the blood and urine pictures, respiratory metabolism and the like, all exhibit the two-fold influence operating in the individual case. Again to illustrate, the thyroid produces aberrations of the respiratory metabolism, the liver affects the carbohydrate utilization. The highly significant part apparently played by focal infections is stressed.

Attention is called to the fact that in no small measure the clinical, and in greater degree the laboratory, pictures simulate those of pituitary dysfunction. Demonstration of hepatic dysfunction constitutes the crucial differential factor. The paper contains illustrative case protocols.

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EXOPHTHALMIC GOITER WITHOUT INCREASED BASAL METABOLIC RATE

ISRAEL BRAM, M.D.
PHILADELPHIA

During the first few years of the popularity of the basal metabolic test for exophthalmic goiter, the procedure was regarded as imperative in diagnosis. It was universally believed that a metabolic rate exceeding plus 10, 12 or 14 per cent was conclusive, and despite the presence of other significant clinical symptoms, the absence of high metabolic readings was generally regarded as indicating the absence of the syndrome. However, during the past several years many clinicians have found it necessary to change their views. Here and there they discover an otherwise typical case of Graves' disease with a metabolic rate distinctly within conventional normal limits. These cases are accumulating because there is more consciousness of the prevalence of Graves' disease and more alertness in its diagnosis.

The present study is based upon a series of 220 cases of Graves' disease characterized by an absence of heightened basal metabolic rate and usually an absence of the customary loss in weight. Our experience indicates that this type of Graves' disease may be divided into five sub-types, viz.: Untreated cases, instances of so-called "burned-out" thyroid, iodinized patients, subtotally or totally thyroidectomized patients, and patients who have undergone excessive roentgen-ray therapy.

Untreated Cases. The description of Graves' disease presenting no increased basal metabolic rate is especially applicable to untreated patients. Though presenting such objective manifestations as exophthalmos and swollen thyroid, these patients as a rule were fairly comfortable for a year or two, hence did not seek medical aid during that time. Aside from the absence of a heightened basal metabolism, the following additional features characterize the symptomatology of these patients:

There is no significant loss in weight; these patients commonly present either a normal or excessive weight.

Exophthalmos is one of the most constant symptoms, and in many patients this is of rather severe form.

Evident thyroid swelling is almost constant. If the patient is obese, an undue layer of adipose tissue over a moderately swollen thyroid gives the exaggerated impression of large goiter. The physical characteristics of the swelling (throbbing, thrill and bruit), are similar to those elicited in typical cases of the disease.

The tachycardia in these patients is usually moderate, though at times the heart rate approaches that observed in the typical form of the disease.

The average subject of Graves' disease without heightened basal metabolism presents a heart rate of 90 to 110 per minute. Especially in early cases the rate may be below 90, while in subjects who have suffered for a year or longer it may reach 120. The force of the heart's action—the pounding against the ribs and the oversensitiveness of the vascular tree to physical and mental excitation are quite typical.

Figure 1. 1. Case of untreated Graves' disease with basal metabolic rate of plus 12 per cent, weight 152 pounds, and pulse rate 120 per minute. 2. A similar case with basal metabolic rate of plus 15 per cent, pulse rate 120 per minute, and weight 150 pounds. 3. Similar case with a metabolic rate of minus 19 per cent, weight 165 pounds, pulse rate 90 per minute.

In other respects the symptomatology of the disease is similar to that observed in typical cases. There is the same emotionalism (though usually in lesser degree), the tremor, the generalized subjective and occasionally objective tremulousness and the fatigue. Sweating, dermographia, and the frequency of arterial hypotension are also observed. Constipation rather than diarrhea is common.

The spontaneous remissions and crises characterizing typical cases are less marked and are inconstant. In other words, the severity of the syndrome as measured by circulatory and nervous phenomena and fatigability is mild to moderate, and the severity as observed at about the twelfth month of the syndrome is prone to continue for several years without marked variations. Occasionally, however, the symptomatology in a case of this sort changes in severity at the termination of the second or third year, becoming typical, with the usual heightening of the metabolic rate and rapid loss in weight, and runs a typical course. This is especially apt to occur shortly after the interposition of a psychic trauma.

TABLE I

CLASSIFICATION OF 220 CASES OF GRAVES' DISEASE WITHOUT INCREASED BASAL METABOLISM

Untreated Cases	"Burned-Out" Thyroid	Iodinized Patients	Subtotal or Total Thyroidectomy	Excessive Roentgen Therapy
74	8	12	117	9

Cases of "Burned-Out" Thyroid. Subjects of so-called "burned-out" thyroid, treated or untreated, present similar characteristics except that the individual is from five to twenty years older and the thyroid gland is atrophied to subnormal size. The syndrome began as typical exophthalmic goiter with high metabolic rate, marked loss in weight and of protracted duration, coursed through several years of crises and remissions and finally "cooled off" as it were. In this process of "spontaneous recovery" (manifested by an unknown percentage of patients) the weight became increased and other manifestations of the disease appeared to become favorably modified. Soon it became evident that the increase in weight was persistent and there appeared other classical features of hypothyroidism or of myxedema. Despite this, however, such residua of Graves' disease as exophthalmos, palpitation, emotionalism, marked fatigability and insomnia persisted. The basal metabolism may vary between zero and minus 20 or 30 per cent.

Cases Following Iodinization. The influence of iodine upon the hyperplastic thyroid is that of converting the organ into the resting stage by the accumulation within the acini of a large amount of colloid substance. This crowds upon the columnar hypersecreting cells and the vascular elements of the thyroid with reduction in its function which may even become inadequate. While the average patient receiving iodine for a long time experiences a partial remission, which is followed in a few

Figure 2. 1. Case of iodinized Graves' disease in 18-year-old girl. The basal metabolic rate is minus 10 per cent; the weight is 185 pounds and the pulse rate is 120 per minute. 2. A similar case with basal metabolic rate of plus 5 per cent; weight, 171 pounds; pulse rate, 94 per minute. 3. A similar case with a metabolic rate of plus 10 per cent; weight, 165 pounds; pulse rate, 120 per minute.

weeks by a crisis uninfluenced by further iodinization, there is observed an occasional exception to this rule, in which prolonged iodine administration results in apparent cure. These individuals present no further heightening of metabolic rate, their weight is normal or above, despite which they may present such residua of the disease as exophthalmos, cardiac "flarability," palpitation, tremor and fatigability in varying degree.

Cases Following Thyroidectomy. Postoperative Graves' disease is common and is present in two forms as a rule. It is characterized either by typical evidences of the disease with normal metabolism, or by a modified form of the syndrome because of superimposition of hypothyroidism or of myxedema. These patients had undergone either a subtotal or total thyroidectomy. Instances of so-called hypothyroidism and hyperthyroidism following radical thyroidectomy are in reality cases of hypothyroidism in combination not with hyperthyroidism but with Graves' symptoms. The basal metabolic rate may vary between plus 10 and minus 40, and the evidences of hypothyroidism may vary markedly and merge into distinct myxedematous symptoms depending upon how much, if any, thyroid function prevails.

Figure 3. 1. A case of persistent Graves' disease with hypothyroid symptoms following thyroidectomy. The basal metabolic rate is minus 19 per cent; the weight is 203 pounds; the pulse rate is 88 per minute. The chief complaints are palpitation, nervousness, insomnia, and fatigability. 2. A similar case with a basal metabolic rate of plus 15 per cent; weight, 150 pounds; pulse rate, 110 per minute.

Figure 4. A case of myxedema with residua of Graves' disease following thyroidectomy. The basal metabolic rate is minus 25 per cent; the heart rate is 82 per minute. The chief complaints are palpitation, pain in the joints and marked fatigability. 2. Case of myxedema with residua of Graves' disease following thyroidectomy. The basal metabolic rate is minus 27 per cent; the weight is 176 pounds; the pulse rate is 80 per minute. The chief complaints are an overwhelming fatigability, palpitation, nervousness, insomnia, despite persistent drowsiness. The extreme exophthalmos is likewise a cause of marked discomfort.

Case Following X-Ray Treatment. Finally, we arrive at those instances of bloodless thyroid ablation performed through overdosage of roentgen rays. The clinical picture here is almost identical with that observed from total thyroidectomy, except that instead of a scar there are

Figure 5. 1. A case of so-called hypo- and hyper-thyroidism, following intensive x-ray treatment for Graves' disease. Under thyroid medication the basal metabolic rate is minus 6 per cent, despite which the pulse rate is 100 and there is distressing fatigability. 2. A case of myxedema with residuae of Graves' disease following ligation supplemented by intensive x-ray treatment. The basal metabolic rate is minus 17 per cent, despite thyroid medication; the heart rate varies between 76 and 94 per minute. The chief complaints are pains in the joints, nervousness, palpitation and distressing fatigability. Observe the telangiectatic areas of the skin over the thyroid. 3. A similar case following intensive x-ray treatment. The basal metabolic rate is minus 22 per cent; the pulse rate is 88 per minute; the weight is 165 pounds. The chief complaints are palpitation, burning of the eyeballs from extreme exophthalmos, nervousness, drowsiness with insomnia and marked fatigability. Observe the telangiectatic spots over the thyroid area.

often seen telangiectatic areas of the skin over the thyroid. In our series of cases the skin over the neck had lost its proper texture, and in many instances had become parchment-like. Deep palpation usually reveals very little thyroid tissue, often a somewhat fibrous band replacing the organ.

TABLE II

METABOLIC FINDINGS IN 220 CASES OF GRAVES' DISEASE WITHOUT INCREASED METABOLIC RATES

	+14% to Above Zero	Zero to —5%	Below —5% to —10%	Below —10% to —15%	Below —15% to —20%	Below —20% to —30%	Below —30%	Total Types of Cases
Untreated Cases	19	23	22	10				74
"Burned-out" Thyroid Treated and Untreated	1	2	3	2				8
Iodinized Cases	2	3	3	3	1			12
Subtotal or Total Thyroidectomy	12	11	10	30	36	11	7	117
Excessive X-ray Treatment			1	1	4	2	1	9
Metabolic Totals	34	39	49	46	41	13	8	220

COMMENTS

These cases indicate that symptoms of Graves' disease may persist in the absence of thyroid hyperfunction. Though possessed of little or no

demonstrable thyroid tissue and rather inadequate thyroid function, yet these patients presented exophthalmos, tremor, palpitation, emotionalism, insomnia, marked fatigability and other evidences of Graves' syndrome often modified by symptoms of hypothyroidism or of myxedema.

It would therefore appear that while the thyroid is probably an almost constant participant in Graves' diesease structurally, almost invariably becoming hyperplastic to some degree, demonstrable hypersecretion is not imperative in diagnosis. The presence of normal weight or overweight in a number of instances was consistent with metabolic findings.

In view of these findings it would appear reasonable to infer that the tachycardia, nervous excitability, exophthalmos, and possibly all the other symptoms of Graves' syndrome are dependent upon factors predominantly other than thyroid excitability, and that we must look to the vegetative nervous system and the other ductless glands for etiological data, thyroid participation being rather tangible in most cases, intangible in some.

SUMMARY AND CONCLUSIONS

1. Two hundred and twenty cases of Graves' disease without an increase above the conventional normal basal metabolic rate and without loss in weight are discussed.

2. Of these, 74 were untreated cases; 8 were of rather protracted duration with so-called "burned-out" thyroid; 12 had been treated with iodine preparations prior to coming under our observation; 117 had undergone subtotal or total thyroidectomy and 9 had received excessive roentgen ray treatment.

3. The data derived from these cases appear to indicate that a high metabolic rate is not imperative in the diagnosis of Graves' disease.

4. It would also appear from this study that Graves' disease is not synonymous with hyperthyroidism, and that the syndrome may occur without demonstrable thyroid excitation.

SOME EFFECTS OF A GLYCERIN EXTRACT OF SUPRARENAL CORTEX POTENT BY MOUTH

PRELIMINARY REPORT

R. G. HOSKINS AND H. FREEMAN*
From the Memorial Foundation for Neuro-Endocrine Research and the Worcester State Hospital
WORCESTER, MASSACHUSETTS

During the past five years we have been engaged in a study of the organic functions in schizophrenia. During the course of the work it has become rather apparent that subjects of this disorder are characterized by a generalized hypometabolism. The depression is manifested in a variety of functions directly or indirectly related to the oxygen metabolism. Among other characteristic features are secondary anemia, low blood pressure, reduced body temperature, and sub-normal oxygen consumption rate. These findings, among others, are suggestive of a condition of chronic, underfunction of the adrenal glands. Convincing differential diagnostic indications of that condition, however, have not been seen.

On a purely empirical basis, we have made various attempts to normalize the organic functions of the patients by the use of various sorts of preparations of adrenal cortex. In a previous publication (1) the negative results obtained in a small series of patients from simple desiccated glandular material were reported. We have had similar negative or equivocal results from other preparations. The following account will deal briefly with certain positive results that have recently been obtained with a glycerin extract of suprarenal cortex.†

METHODS

The adrenal preparation was supplied in pill form, each pill representing 10 grains of the fresh cortex. The glands were collected from freshly killed beef animals and usually kept from 24 to 48 hours at about zero temperature while a supply adequate for a "run" was being accumulated. All glands presenting an abnormal appearance were discarded as was the adhering tissue fragments and fat from those that were used. The medulla was then removed by hand trimming. The material was kept on ice except during the sorting and trimming process. The cortex material was finely chopped, mixed with glycerin and macerated with frequent stirring for two weeks. The liquid portion was strained off and the insoluble residue washed with distilled water. The original liquid and washings were combined and concentrated by evaporation at low temperature

*With the collaboration of the Research Staff of the Worcester State Hospital.

†We are indebted to Mr. Ronald Helps of the firm of Schieffelin & Co. of New York for generous supplies of the preparation used.

to a syrupy consistency. To this was added an indifferent excipient, after which the material was moulded and coated with gelatin.

Ten patients (male adults) were selected for study, primarily on a basis of low systolic blood pressure. After a week of preliminary observations they were given the adrenal cortex in divided doses three times per day. The dosage was gradually increased in accordance with the schedule shown in Table I.

TABLE I

Weeks	0	1	2	3	4	5	6-10	
Dosage*	0	9	9	18	27	36	45	4 patients
Dosage	0	9	18	27	36	45	45	6 patients

*In pills per day, each pill representing 10 minims (0.6 cc.) of extract, representing in turn an equivalent weight of fresh gland.

During the first week and at intervals during the test period, a variety of observations were made. These included, once a week, weight, red and white blood cell counts, differential leucocyte counts, a determination of the Schilling leucocyte formula, the hemoglobin in grams per 100 cc. by the Haden-Hausser method, basal oxygen consumption rate, basal systolic and diastolic blood pressures, pulse, rectal temperature, and respiratory rate. Both the systolic and diastolic blood pressures were obtained by two observers working independently. The set of values that was used in the accompanying graph was obtained in the wards in the morning before the patients had arisen. A second set, which rather closely corroborated the first set, was obtained in the basal metabolism laboratory in connection with oxygen consumption readings. Four times during the course of the experiment twenty-four-hour samples of urine were collected and from these were determined the total volume, total nitrogen, urea nitrogen, and creatinin. There were also calculated the total urinary solids and the residual nitrogen. Twice during the course of study the blood was analyzed for several chemical constituents, including nitrogenous bodies, reducing bodies and cholesterol. Standard laboratory methods were used throughout. The more difficult procedures were performed by professional chemists or physicians and the other procedures by well-trained technicians under constant supervision.

RESULTS

While suggestive trends were shown in a number of other features, this paper will deal for the most part with only four functions in which the results seemed most significant. Without further elaboration of the point, it may be stated that the consistency was of such order that the results are of high statistical validity despite the small number of cases included. The probability of the findings having been due merely to the operation of random chance is something of the order of one in one thousand.

The urine. With remarkable regularity a diphasic reaction was shown in the volume of the urine and in its composition as regards the nitrogenous bodies. For example, the volume increased from an average of 2542 cc. to a value 38 per cent higher, then fell off to a level 14 per cent above the initial value. Similar increase followed by decrease was shown by the total solids, total nitrogen, urea nitrogen, and creatinin. Since, however, there was considerable variability among the individual cases, merely passing mention will be made of the trend of this phase of the work. It is hoped to extend the tests sufficiently to permit recognition of the law that seems to be operative here.

The blood picture. There was in general an upward trend in the white cell counts but with lymphocytes at the end falling off to a level below that at the beginning. The erythrocytes, as shown by Fig. 1, manifested a rather consistent rise throughout almost the entire period.

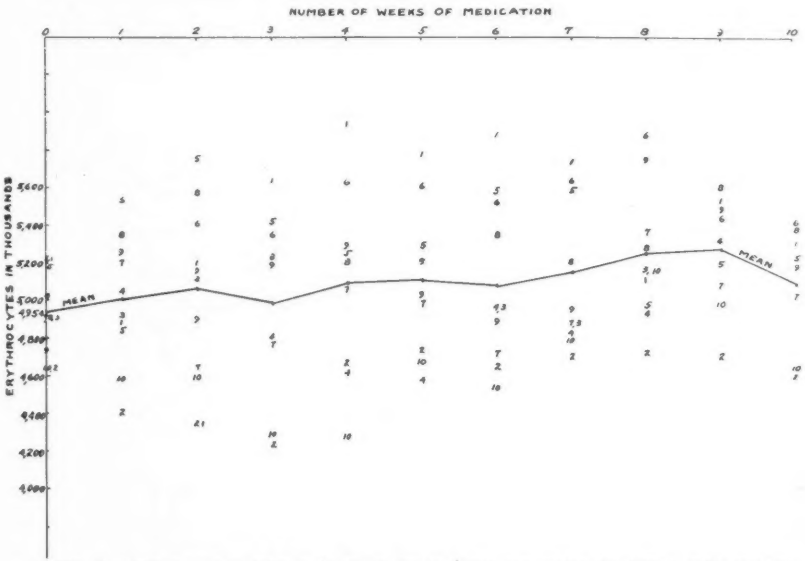

Fig. 1. The average erythrocyte count on ten patients under treatment with cortical extract. The values given are those obtained at the end of each week recorded. The values for the individual patients are indicated by the Arabic numerals.

The average count at the beginning of the study was 4,954,000; at the end of the ninth week it had risen to 5,280,000, but during the last week there was a falling off to 5,100,000. Whether this represents a true diphasic reaction, such as Hoskins and Jellinek (2) have recently reported for thyroid medication, cannot be determined without further study.

The blood pressure. As previously stated, the patients were selected for the study primarily because of an initial presenting hypotension. As shown by Fig. 2, the average systolic reading during the "zero" week was

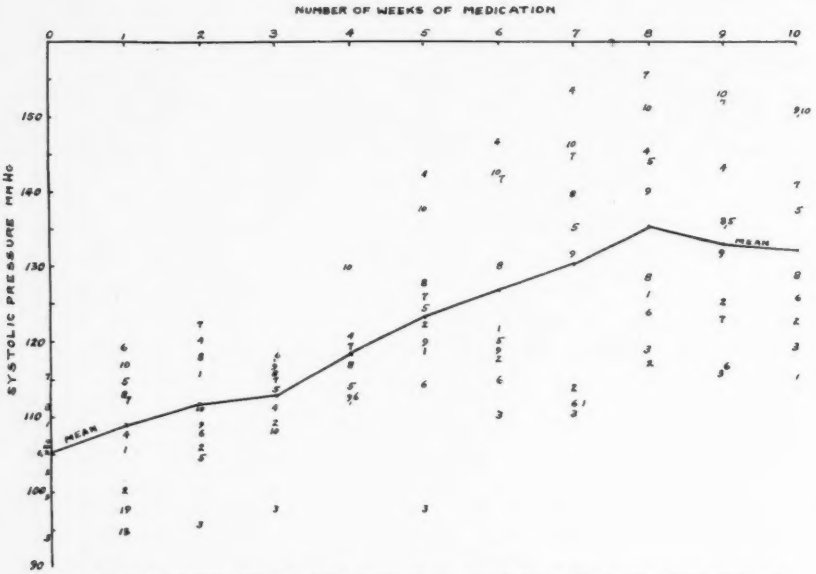

Fig. 2. The average systolic blood pressure on ten patients under treatment with cortical extract. The values given are those obtained at the end of each week recorded. The values for the individual patients are indicated by the Arabic numerals.

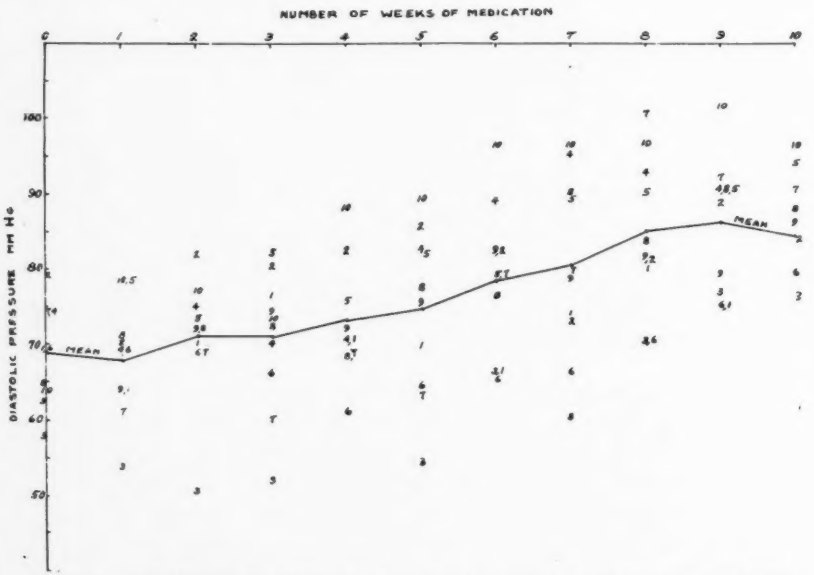

Fig. 3. The average diastolic blood pressure on ten patients under treatment with cortical extract. The values given are those obtained at the end of each week recorded. The values for the individual patients are indicated by the Arabic numerals.

105.7 mm. Hg. The pressure gradually increased, though with apparently characteristic secondary fluctuations in the individual curves, until, at the end of the eighth week, it was 135.2 mm. It then fell off at the end to 132.5. A study of the graph will show that there was no exception to the general trend. The diastolic blood pressure went through a similar course with the secondary fluctuations in general synchronizing with those of the systolic pressure. The initial level was 69 mm. The highest point reached was 86, and the experiment closed with the pressure at 84 mm. (Fig. 3).

The weight. As shown by Fig. 4, the mean weight improved throughout the course of the study. The average at the beginning was 62.6 kgm. and at the end, 65.4 kgm. This difference, while it would not be strik-

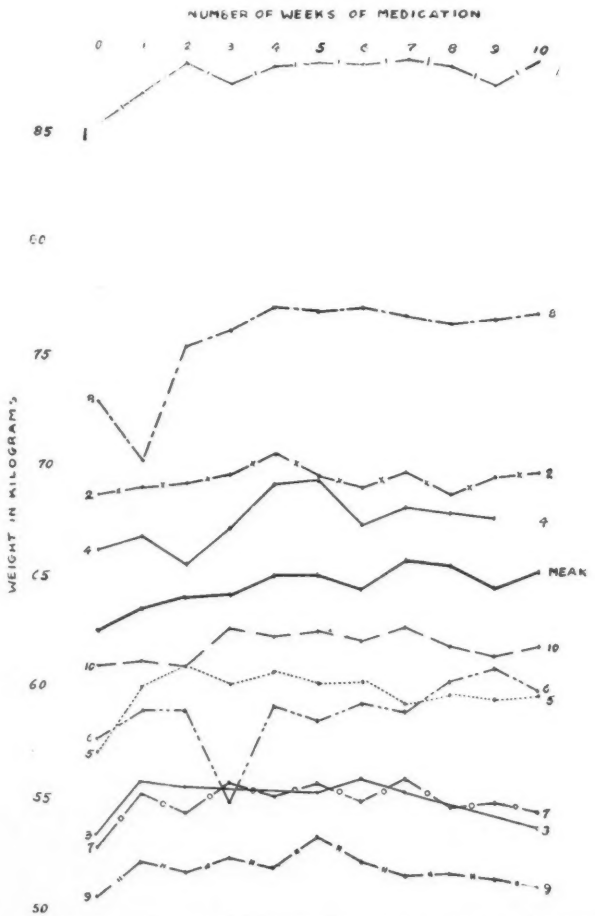

Fig. 4. The average and the individual weights of ten patients under treatment with cortical extract. The values given are those obtained at the end of each week recorded.

ing in degree for ordinary subjects, is rather impressive in that we were dealing with schizophrenic patients. On numerous occasions we have attempted, for therapeutic reasons, to increase the weight and have found this to be rather difficult of accomplishment. It will be noted from the graph that although rather marked irregularity was shown in the curves of the individual patients, each was heavier at the end than at the beginning of the study.

The blood chemistry. No very striking changes occurred in the composition of the blood. There was noted, however, a general tendency of the nitrogenous bodies to decrease slightly in amount. More data will be needed to determine whether such changes as were seen are of statistical validity.

The oxygen consumption rate. There was a strong suggestion of a diphasic effect in the rate of oxygen consumption. Early in the study period, under the influence of low dosage, the average rate dropped from 87 to about 84 per cent of normal prediction. At the end of the sixth week the rate had risen to an average of 92 per cent of normal but the rise was not sustained, and the experiment terminated with the rate at the initial level. This aspect of the problem demands further study.

Since the foregoing data were compiled the patients have had a rest period without medication. The blood pressures have fallen off and are now at approximately the same levels shown at the beginning of the study. The other features have not yet been adequately restudied.

DISCUSSION

Those familiar with recent developments in the field of adrenal cortex physiology will recognize that the results of this study are in general comparable with those that are being obtained from cortin and other concentrated extracts. Since the study was completed, Rogoff (3) has published certain clinical results from the use of his preparation "interrenalin." It would seem probable that his extract is closely similar, both in composition and potency, to that which we employed. His report, however, included so little information on the physiologic effects of the extract as to leave somewhat uncertain the question whether his method of extraction secures precisely the same active principle or principles as those with which we were dealing.

Britton (4) has recently determined that adrenal cortex extract is only about one-fourth as potent when given by mouth as when administered parenterally. It would seem, therefore, that simple glycerin extraction is an unusually effective method of securing the active principle of the adrenal cortex—assuming that we were dealing with the same hormone as that contained, for example, in cortin. The latter is given to human subjects in dosage representing an ounce more or less to several ounces

of the fresh cortex per day, whereas, our largest dosage was slightly less than an ounce and this was administered by mouth.

As is well known, extracts of adrenal cortex prepared from hand trimmed material contain a trace of adrenine. In view of the facts, however, that this hormone is of very low potency when administered by mouth and that the effects are evanescent, it is extremely unlikely that adrenine played any part in the findings reported.

Whether the results secured were non-specific or whether they indicate that schizophrenia is characterized by adrenal deficiency cannot profitably be discussed until further data are secured.

SUMMARY

Ten schizophrenic patients initially presenting low blood pressure were treated for ten weeks with glycerin extract of adrenal cortex.

The dosage was gradually increased from an equivalent of about 100 grains (6.5 gm.) to 450 grains (29 gm.) of fresh gland substance per day.

The systolic blood pressure was increased in all cases. The average initial pressure was 105.7 and the final pressure 132.5 mm. Hg. Similarly the diastolic pressure was increased from 69 to 84 mm. The blood pressure returned to approximately the initial levels after treatment was discontinued.

There was an irregular increase in the weight from an average of 62.6 kgm. at the beginning to 65.4 kgm. at the end.

There was also a fairly consistent increase in the red cell counts of about 300,000 on the average per patient. At the end the increase had fallen to about 150,000 cells above the initial level.

There was evidence of early stimulation of renal function with later return toward initial levels.

There was an apparently significant increase in the oxygen consumption rate but this was not sustained.

There was a slight downward trend in the nitrogenous bodies of the blood.

The investigation is to be extended.

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MULTIPLE GLANDULAR SCLEROSIS

ADDISON'S DISEASE AND BASEDOW'S DISEASE

DR. KARL HERMAN
SUBOTITZA, JUGOSLAVIA

In the domain of internal medicine there are still many problems awaiting solution. Within its narrower limits, particularly in the field of endocrinology, there is no lack of such unsolved problems. By reason of the fact that not merely one gland but a group of glands may be simultaneously affected, there sometimes arises such a combination of symptoms and forms of diseases that the clinician is confronted with a task of almost insuperable difficulty. Though rare, pluriglandular forms of endocrine disease have been described by French and Viennese authorities. The fact that cases of this kind are so seldom reported in medical literature is not to be wondered at; they are not only rare but are also extremely difficult to diagnose.

The writer has recently reported such a case (1). A second case now under study is herewith recorded.

The patient, a woman aged 53, has been gravely ill for about two months. Her illness began with extreme weakness, emaciation and loss of appetite. Soon she had not only no desire for food but vomited whatever she had eaten. Soon she noticed an increase in the size of her neck, the thyroid became enlarged and, simultaneously, her eyes appeared larger and more glittering. Palpitation and more violent action of the heart prompted her to see a physician, who diagnosed the condition as Basedow's disease. This exophthalmic goitre was treated by means of insulin injections and roentgen irradiation, after which the patient's condition showed a slight improvement; she felt somewhat stronger, the appetite began gradually to return and the general condition improved. About three weeks after this improvement I saw the patient, whose condition at that time was again very serious.

Her most troublesome symptom was nerve-racking insomnia, which even the strongest hypnotics failed to overcome. In the 24 hours the patient slept scarcely 1-2 hours, so that she used to feel unusually tired and exhausted; her face was drawn with suffering and she had lost her appetite. Vomiting occurred 5-6 times daily, mostly after meals, but frequently also on an empty stomach. According to the statements of her relatives the patient was often delirious, and incontinentia urinae et alvi occurred, of which she was unaware. When conscious she really did not know what was the matter with her. Considerably more serious were the patient's symptoms of wasting, a suffering expression of countenance, restlessness and insomnia. Skin and mucous membranes were anaemic, the eye glittering; the eyelids did not quite cover the sclerae, and a slight exophthalmos was noticeable. Her hair had fallen out in quantities; her eyebrows were normal, but the hair in the axillae was missing entirely. The hair in the genital region was not affected. The thyroid gland was enlarged and showed a visible pulsation, particularly the right lobe. As regards the breasts, no pathological change was found. The heart beats were normal, the heart sounds clear, the pulse frequent, the rate being 96 per minute. As to the spleen and the liver, no change could be found. Occasionally the patient complained of pain in the region of the stomach, which did not, however, appear to be intense. The appetite was completely lost, and vomiting was of frequent occurrence. The movement of the bowels was irregular. As regards the nervous system, an extreme degree of insomnia was present, together with restlessness, inclination to cry, and occasional loss of consciousness. The last-named symptom either

merged into apathy or became manifest in the form of intense excitement. For the rest, the reflexes were regular: no appreciable deviation was evident and the pupils were normal. The Babinski reflex was normal; the blood sugar was 112; the blood pressure, 135 mm. Hg.; the leucocyte picture, normal. The red blood cell picture showed the presence of severe secondary anaemia. X-ray photographs showed the stomach to be normal, the lungs clear, both hili darkened and enlarged, both pleurae laterally fixed and thickened. The x-ray photograph of the suprarenal region did not reveal any pathological shadow.

Figure 1. Patient with multiple endocrine sclerosis before treatment with specific hormone.

Figure 2. The same patient after treatment with adrenal cortical hormone.

These serious symptoms cannot be accounted for by Basedow's disease alone. The Basedow symptoms were not at all severe, the struma only moderately large, the exophthalmos below the average, the pulse not remarkably frequent. The patient never perspired, the skin was remarkably dry and pale, no pigmentation was anywhere visible. The disparity between local and general symptoms was so striking that it could not be overlooked.

Thus the main question was: What is the essential nature of this disease, and what is the cause of the serious decline in the patient? Is it Basedow's disease alone, or this in conjunction with some other ailment? If the latter, which of the two diseases is the more important? It was therefore necessary to ascertain the nature of the other disease in question. One thing was clear: that the patient was suffering from a cachexia due to an endocrine disturbance. Accordingly, those endocrine glands, any affection of which generally causes cachexia, had to be considered. These comprised the pancreas, hypophysis, thyroid, parathyroid, suprarenal capsules, and ovaries. Of these the thyroid could not be regarded as the determinative factor, since it had been found to be relatively mildly affected. Nor could the pancreas, as the patient was not suffering from diabetes. While the parathyroid may indeed lead to cachexia, owing to

excessive or defective functioning, there was no such indication in this case: the nervous system showed no symptom of tetany, nor the bone structure any sign of osteitis fibrosa. The ovaries, as endocrine organs, could not give rise to any serious disorder, the patient being 53 years of age. Thus only two endocrine glands remained for consideration: the hypophysis and the glandula suprarenalis. The symptoms present could not be associated with either of these two possibilities. Loss of hair and absence of hair in the armpits occur in disease of both glands. A high degree of anaemia and an alabaster-colored skin may be present in Simmonds' disease as well as in Addison's disease. The poor state of the teeth seemed rather to indicate Simmonds' disease, yet this is not a decisive symptom. In addition, the patient's intense restlessness and excitement decidedly negatived the presence of Simmonds' disease, these being symptoms which might have been attributed to Basedow's disease if the other Basedow symptoms had not been comparatively mild. The sufferer from Simmonds' disease is, in fact, calm, quiet and silent, avoiding all movement as far as possible; his temperature is low and frequently even subnormal. The symptoms observed in the present case were of a diametrically opposite nature. The possibility of a Simmonds' cachexia was therefore rather uncertain. Accordingly, the possibility of an Addison cachexia had to be considered, but here, too, the symptoms could hardly be attributed to this disease. Above all, the surest sign of this disease was absent, *viz.*, pigmentation. Other negative signs were the blood pressure (135 according to Riva-Rocci's test) and the blood sugar value (likewise normal). On the other hand, a high degree of auto-intoxication, anaemia, gastrointestinal troubles and the highly excitable condition of the nervous system seemed rather to indicate Addison's disease. To clear up this question the patient was given Prolan, as experience had shown that the administration of the hormone from the anterior lobe of the pituitary had effected a rapid improvement in cases of Simmonds' disease. In the present case no improvement occurred, this being in itself a strong argument against the presence of Simmonds' disease. As the possibility of the morbus Addisoni became increasing apparent, I used a specific hormone which is produced in America by Swingle and Pfiffner. Fortunately, at this time the Gedeon Richter Chemical Works, Budapest, announced that they had succeeded in extracting the hormone of the adrenal cortex. At my request, I was immediately supplied with the desired quantity of hormone—a favor for which I desire here to express my sincerest thanks. This hormone which contains the active principle of the suprarenal cortex is sold under the name Cortigen.

The first striking result was that the patient—apart from a few interruptions—slept almost continuously for three days. Not being quite clear at first as to the cause of this prolonged sleeping, I thought of coma, but when we saw that the patient was brighter on waking, the matter was explained. From now on her condition improved: the vomiting ceased,

food could be assimilated and the extreme excitability of the nervous system soon disappeared. The patient no longer talked incoherently or tossed restlessly about the bed; she ceased to moan and groan. Evacuation of the bowels and micturition were normal, while the stools and urine could be retained within the necessary limits. In short, the severe auto-intoxication disappeared under the action of Cortigen injections. The patient, who previously vomited six times on the average and took scarcely any food, now ate six times and vomited not at all. In six weeks her weight increased about 9 pounds, the anaemia improved and the features recovered their composure. Even after two weeks' Cortigen treatment the patient, who had frequently been delirious before the treatment, was able to read the newspaper and slept quietly at night. No sedative of any kind was now necessary, also no insulin—which, moreover, had been of no effect. The patient grew fuller in the face and body and this improvement still continues. The body weight increased from 84 pounds to 95 pounds, and will no doubt go on increasing, thanks to Cortigen. One thing is an established fact: that the action of Cortigen in this case has been most remarkable. Anyone who has seen how a patient suffering so terribly and wasted to such a degree has been, as it were, transformed within a few days; how restlessness has been turned into rest, sleeplessness into sleep, lack of appetite into hunger, and vomiting into normal digestion—anyone who has seen this can never forget it. The hormone derived from the cortical layer of the suprarenal capsule and the prompt action of this preparation had, accordingly, settled the question: The patient was suffering not only from Basedow's disease, but also from Addison's disease to a very high degree, this being speedily influenced by the hormone. In this case, therefore, Cortigen has proved of excellent service both as an aid to diagnosis and as a remedy. Its action is not less certain than that of insulin in diabetes or the action of hypophysis (anterior lobe) in Simmonds' disease.

As the action of the cortical substance is not yet understood, it would be important to know in what way this hormone action is caused. Recent investigations afford an indication in this direction. Zwemer and his fellow-workers have proved that in the blood the diminished carbon dioxide tension is increased, as are also the chlorides and sugar in the blood. The turgor of the tissues and the number of erythrocytes in the blood are increased. Above all, an improvement is effected as regards the gastric auto-intoxication, so that the authorities in question have tried this hormone also in cases of gastric and intestinal auto-intoxication in infants, very favorable results being obtained. Probably its use is not confined to this narrow field and it may be possible to employ it also in other diseases, while the additional experience to be gained by the use of this hormone will enable the picture of Addison's disease to be rendered more complete. In many cases we shall rightly diagnose this disease, although we should never have thought of it before, especially in cases where pigmentation is absent. The researches of Szent-Györgyi are of fundamental importance

in this field. They have proved, *inter alia*, that the cortical layer of the suprarenal capsule contains a specific substance, the so-called hexuronic acid, the presence of which checks the pathological pigmentation, while its absence promotes such pigmentation. It is not surprising, therefore, to observe bronze-colored patches in one patient and not in another, as Szent-Györgyi's researches have proved that the absence of hexuronic acid is not a necessary symptom of Addison's disease.

Nor, moreover, is low blood sugar tolerance or hypotension an integral symptom of this disease, as these phenomena are due to an affection of the medullary substance and not of the cortical layer. The clinician must therefore modify in a certain respect his diagnosis of Addison's disease; although the latter symptoms are certainly a help in certain cases, their absence is not an infallible argument against the presence of this disease. Anyone, therefore, who is inclined to diagnose Addison's disease simply where blood pressure, blood sugar tolerance, and pigmentation show a deviation from the normal, will in many or in all cases fail to recognize the disease from which the patient is suffering—this being now, in this age of hormone treatment, a grave mistake. The most important diagnostic sign is the improvement which sets in after the administration of Cortigen in cases of this disease, the symptoms of which are not yet sufficiently understood, although the movement of the carbon dioxide tension proceeding physiologically in the blood, the movement of the blood sugar and the number of erythrocytes give an approximately correct idea of the specific hormone action. Hartman and Swingle and Pfiffner were the first to produce the cortex hormone in a practical form. According to Hartman the effect on human beings as well as on animals appears within a few hours, namely an improvement in the somatic condition and a reduction of the high content of urea in the blood; dehydration ceases and the turgor increases.

It is interesting to note that our patient in about the sixth week of the Cortigen treatment developed oedema in the ankle which did not respond to digitalis. At first its origin could not be explained, although it had nothing whatever to do with cardiac weakness. Much later, when the dose of Cortigen was reduced from 4 ampoules to 2 ampoules daily, the anasarca disappeared spontaneously. This is probably identical with the anasarca which occurs in insulin treatment, the cause being the excessive dosage of the hormone. From the practical standpoint it is important that this phenomenon should not be regarded as a sign of cardiac weakness, but as an effect of the hormone, which disappears when the quantity of hormone administered is suitably reduced. This question gives rise to another problem: How and in what amount should the hormone be administered? It is difficult to answer at this stage. The American authorities observed a pronounced improvement in a very few hours. From this it follows that one ampoule may be given several times a day. From his own experience the writer can state that in very severe cases 2-3 ampoules

of Cortigen a day are sufficient; when improvement sets in, this quantity can be reduced to 2 ampoules and afterwards to one ampoule a day.

My patient, who ultimately found the injections troublesome, broke open the ampoules and drank the contents. At present she is taking weekly the contents of 3 ampoules in a little water and feels that this agrees with her; her bodily strength is invariably good, and for the time being there is not the slightest sign of a relapse.

Hitherto, so far as I know, no cases or only very few have been reported in Europe as being cured by a specific hormone treatment. In American medical literature a large number of such cases have already been communicated (from the Mayo Clinic by Rowntree, from Buffalo University by Hartman, from Princeton University by Swingle, and others). I am of the opinion that the hormone of the suprarenal cortex, Cortigen, is an excellently effective remedy for Addison's disease, and also an extremely important aid in its diagnosis. Only a few years ago, Rowntree recommended the "postural hypotension" in diagnosing Addison's disease where pigmentation is not present, *i.e.*, demonstrating the alteration in blood pressure which occurs in passing from the vertical to the horizontal position. In my opinion this is only a finer form of blood pressure examination which in the case of Addison's disease is only concomitantly positive, as it indicates an affection of the medullary substance and not of the cortical layer. On the other hand, the favorable reaction to the hormone is a certain symptom. It is important that we should in future thoroughly understand the pharmacological action of the hormone, of which at present we have only a rough idea. It is also of the utmost importance that the hormone be graded so as to form exact units—a desideratum which is likely to be shortly fulfilled. So long as Addison's disease is atypical and without dependable symptoms in its occurrence it is the duty of the physician, in cases of obscure cachexia, to employ also the cortex hormone until it is quite clear whether the organism requires it or not. According to American authorities this question can be decided within a few hours; I am also of the opinion that within two days, at the latest, it is possible to decide whether the illness is or is not due to deficiency in the cortex hormone. In definite cases the patient becomes quieter and sleeps better, consciousness is clearer and vomiting subsides.

At all events, the cortex hormone (Cortigen, Cortin) represents another great achievement in medical research, and its fundamental significance is not inferior to that of insulin. It is quite possible that henceforth no one need die of Addison's disease. Its field of use will probably be restricted to those cases in which a high degree of irritability of the nervous system, severe gastric and intestinal disorders, anaemia, adynamia, or pathological pigmentation play a part. These include: Bronzed diabetes, delirium due to alcohol, morphine or cocaine, chlorosis resulting from attacks of gastritis, persistent colitis, enteritis, or protracted convalescence. Finally, it should be borne in mind that in the case under review not only

a severe form of Addison's disease but an exophthalmic goiter (Basedow's disease) has also been present, and that the cortex hormone has given splendid results even in such an especially severe endocrinous condition.

SUMMARY

The case is reported of a woman who was diagnosed as suffering simultaneously from Addison's and Basedow's diseases. The case was characterized by extreme weakness, emaciation, vomiting, thyroid enlargement with visible pulsation and prominence and glittering of the eyes. Intractable insomnia, delirium and incontinence were prominent symptoms.

Under treatment with adrenal cortex hormone remarkable improvement at once ensued. This was initiated by three days of sleep, following which the delirium, the vomiting, the incontinence and the anemia improved. The patient gained nine pounds weight in six weeks.

The problem of differential diagnosis is discussed and the use of cortin is recommended as a diagnostic method.

ADDENDUM

The patient, after a year of treatment, remains well. She is able to carry on her household duties and enjoys satisfactory body strength.

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CHRONIC ADRENAL INSUFFICIENCY PRODUCED BY CAUTERY

FRANK A. HARTMAN
From the Department of Physiology, University of Buffalo
BUFFALO

Many attempts have been made to produce chronic adrenal insufficiency. A review of the earlier work is given elsewhere (Hartman). Ligation of a part of the blood supply was used with some success in earlier work. Rogoff recently by the use of this method has succeeded in greatly prolonging the survival period after operation. Symptoms of adrenal insufficiency were observed at intervals.

More than two years ago we started a series of experiments on cats in which the adrenal medulla was destroyed, in order to note the behavior of such animals over long periods. Certain observations which appear to be significant are here reported.

We tried splitting open the ends of both adrenals and then removing the medulla by a sharp scalpel. The adrenals of the two cats thus operated upon were examined at 272 and 321 days, respectively. Both adrenals contained good medullary tissue in each instance.

Destruction of the medulla by electric cautery proved to be more effective. This was done through one pole of the gland. In forcing a path to the medulla and in the extensive destruction of tissue on the interior of the gland worked upon, much cortex was destroyed.

Operations were carried out with the usual aseptic precautions. A record of the daily food consumption and frequent weighings was kept.

At the termination of the experiment, the adrenal tissue was examined in most instances histologically after fixation with formaldehyde potassium bichromate solution, staining with haematoxylin and Sudan III and sectioning with a freezing microtome. In some instances the tissue was weighed but on account of the dead or connective tissue, the values obtained were usually much too high, as an indication of active tissue. Measurements of the adrenal glands gave, for the same reason, exaggerated values.

Both Medullae Cauterized

The medullae in both adrenals were cauterized in two stages from a few days to several weeks apart in 23 cats. The death of six animals was attributed to respiratory infections. These, however, survived from 14 to 55 days.

Ten animals were killed, all but one having gained weight. This one had lost 26 per cent (from 3610 gm.) at 349 days, the time of death. One adrenal was nearly all destroyed; the other contained good cortical tissue

but very little medulla. A second cat gained 61 per cent in weight (from 2200 gm.) in 151 days. At the time of death (306 days) the adrenals appeared to be about normal in size with both medulla and cortex in the left but little medulla in the right. In a third (killed at 369 days), although both adrenals were present, they were composed of only an outer shell of healthy tissue. The adrenals appeared normal in a fourth. In a fifth killed at 113 days the right adrenal weighed 0.111 and the left 0.134 gm. Those in the remaining five were not examined (killed at 90, 131, 137, 160, and 162 days, respectively).

Seven animals apparently died of adrenal insufficiency. The accompanying table (I) shows that the survival period of five was much longer

TABLE I

MEDULLAE OF BOTH ADRENALS CAUTERIZED

Cat	Sex	Survival Days	Adrenals	Body Weight		
				Original	At Death	Per Cent Loss
LM	F	32	One adrenal remained 7x4 mm., contained small piece of medulla and good cortex with moderate lipoid	2340	1204	48.5
LO	M	23	Left adrenal, 0.366 gm. Right adrenal, 0.046 gm. No medulla in either. Lipoid present	2700	1720	36.3
LQ	F	57	Left adrenal, 0.190 gm. Right adrenal, 0.122 gm. Lipoid present	2800	1320	52.9
LR	M	9	Right adrenal destroyed. Left adrenal, good cortex present	3200	2280	28.8
LS	F	12	Few medullary cells and lipoid in each adrenal	2900	2160	25.5
MB	F	40	Small piece of medulla in right adrenal; masses of lipoid in cortex of both glands	1720	1080	37.2
MY	F	315	Both medullae with active tissue. No healthy cortex seen	3700	2540	31.4

than the average for adrenalectomized cats. This would indicate that the vital hormone was being produced by the remaining cortical tissue. The production of the hormone, however, was inadequate for indefinite survival. The great loss of weight is typical of chronic adrenal insufficiency. Gingivitis developed in two animals (LM and LR) and gastric ulcers were found in one (LM). Otherwise there was nothing remarkable to be seen post mortem. Histological examination of the adrenal tissue demonstrated the presence of healthy cortical tissue in every case but MY, which was doubtful. The total amount of cortex, however, was much reduced in every instance. Sometimes the active tissue as indicated by the presence of lipoid was limited to patches. A small amount of apparently active medulla was found in four animals as indicated in the table.

In these seven animals regeneration of cortex, if it occurred, was inadequate.

One Adrenal Removed, Medulla of Other Adrenal Cauterized

In another series of 14 cats (Table II), the right adrenal was removed and then several days later the medulla of the left gland was cauterized.

TABLE II

ONE ADRENAL REMOVED, MEDULLA OF OTHER CAUTERIZED

Cat	Sex	Survival Days	Body Weight			Post Mortem	Adrenal
			Original	At Death	Per Cent Loss		
KP	M	72	2300	1970	14.3	Gingivitis.	3.5x3 mm. Trace of medulla. Lipoid confined largely to outer zone of cortex.
KQ	F	54	2450	2350	4.1	Gastric ulcers.	
KR	M	66	3200	2360	26.3	C2*—Slight gingivitis.	5.5x4 mm. Medulla absent. Cortex healthy, but small amount of lipoid.
KS	M	60	3900	3000	23.1	C1*—Gastric ulcers.	6x4 mm. Half of gland dead. Small piece of medulla. Small amount of lipoid in cortex.
KU	M	66	3700	3300	10.8	Gingivitis. Gastric erosions.	8x5.5 mm. Central core dead, medulla absent. Lipoid abundant in cortex.
KV	M	23	2600	1500	42.3	Gingivitis. Incisors loose.	5.5x4.5 mm. Weight .18 gm. Large core of dead tissue. Lipoid abundant in cortex.
KW	F	43	2600	1570	39.6	C4*—Slight gingivitis, pin point gastric ulcers.	5x3.5 mm. Weight 0.178 gm. Core dead. Medulla absent, lipoid abundant in cortex.
KX	M	40	3510	2970	15.4	C1*—Slight gingivitis.	6x4 mm. Small piece of medulla remained, lipoid present in cortex.
KZ	F	8.5	2220	1750	21.2	Gingivitis.	Considerable amount of cortex remained with lipoid present.
LA	M	6	2200	1800	18.2	Nothing remarkable.	Destroyed.
LB	M	65	3900	2500	35.9	About half of stomach ulcerated.	7x4 mm. Cortex appeared normal except little lipoid.
LC	M	28	2500	1400	44.0	Three small gastric ulcers.	Cortical tissue weighed .079 gm. Appeared healthy.
LJ	F	55	2500	2270	9.2	C2*—Slight gingivitis. Gastric ulcers.	
LK	M	144	3040	2700	11.2	Nothing remarkable.	Medulla absent, lipoid of cortex much reduced. Weight 0.214 gm.

C1*—Convulsions day of death.
C2*—Convulsions two days before death.
C4*—Convulsions four days before death.

All but two of these animals survived 23 days or longer; the longest period was 144 days. All cats eventually showed loss in weight. In some this was considerable. Five showed an increase in weight after the second operation, to lose later and finally die. KP weighed 2785 gm. at 48 days, after

cautery of the remaining adrenal, KQ weighed 2637 gm. at 39 days, KU weighed 3735 gm. at 38 days, LJ weighed 2870 gm. at 39 days, LK weighed 3400 gm. at 125 days. In these animals that gained over their original weight, hormone production in the adrenal cortex must have been adequate at the time. Later the hormone production of all must have been inadequate because they died with indications of adrenal insufficiency. Five of the fourteen had convulsions before death. One-half of them had erosions or ulcers in the stomach. The adrenal tissue found at autopsy was small and gave little, if any, evidence of hypertrophy. A very small amount of medullary tissue was found in three of the twelve animals examined. The dimensions and weight of the adrenal almost always gave an exaggerated idea of the active tissue because so often dead tissue could not be separated from the active tissue. The striking thing is that all of the animals died within five months.

In a control series, we attempted to destroy as much cortex without injuring the medulla, as was destroyed in the experiments on medullary destruction.

Cortices of Both Adrenals Cauterized

The cortices of both adrenals were cauterized in two stages. Six cats were so operated upon. All but one were sacrificed 222 to 286 days after the second operation (Table III). This one was sacrificed at 49 days. The

TABLE III

CORTICES OF BOTH ADRENALS CAUTERIZED

Cat	Sex	Killed	Body Weight			Adrenals
			Original	At Death	Maximum	
OA	F	286	2400	2300	3020 at 39 days	Both very small—outer zone healthy, rest connective tissue.
OE	F	231	2980	2600	3280 at 63 days	Right about half size. Left very small. Both cortex and medulla present.
OK	M	229	2100	2900		Not examined.
OM	M	225	4010	3050	4300 at 54 days	Both healthy. Stimulation of left splanchnic caused marked increase in rate of denervated heart.
OT	M	222	3540	3150		Right fibrous mass 6x4 mm. Left 14x9 mm. Both cortex amd medulla present.
OX	M	49	3210	2980		Not examined.

animals were in good condition. Five had lost weight at the time of death. Three of these had gained weight at one stage to lose it later. One or both of the adrenals were very much smaller than normal in three of the four animals examined.

DISCUSSION

It has already been pointed out that there was little evidence of hypertrophy of adrenal tissue in our animals. Although the methods for estimating the amount of active tissue were not very satisfactory, any considerable hypertrophy would have been detected. The amount of active tissue remaining was sufficient to prolong the survival periods of the animals several weeks. If hypertrophy occurred it was insufficient to supply the minimal requirements for existence. A few of the cats with both medullae cauterized showed a ravenous appetite and a remarkable gain in weight. It might be suggested that this was due to an increased output of cortical hormone. The same animals later lost weight. If such an explanation holds, the overactivity of the cortical tissue might later lead to failure and thus a loss in weight.

Why did hypertrophy fail? Possibly the great demand placed upon the remaining tissue exhausted it so far as to check hypertrophy. Hypertrophy of adrenal tissue has been repeatedly described by various authors (Goldzieher, Kojima, MacKay and MacKay, and MacKay and Polland). Usually in these experiments one adrenal was left intact after the removal of the other. In such a case the load placed on the active tissue was not so great.

Cauterization hardly accounts for the failure to hypertrophy unless the attendant destruction of the blood supply and scar tissue formation were responsible. On the other hand, a tissue which hypertrophies easily like the liver is said to be difficult to reduce in amount because of this power.

It would appear from our experiments that the adrenal tissue remaining after cauterization in the cat does not hypertrophy readily. This raises an important question clinically: how easily does active adrenal tissue left from disease hypertrophy? From our experiments on cats it appears that when only a small amount of active tissue remains it does not increase sufficiently for compensation. Whether it could do so if it were spared by the injection of cortical extract remains to be seen.

The survival of all cats with cortex cauterized and the death of some of the cats with medullary cauterization may possibly be accounted for by escape of a greater amount of cortical tissue in the former. Extensive cauterization of the medulla not only destroys a large amount of cortex directly but may indirectly injure cortex by destruction of the blood supply more than would occur from peripheral cauterization of the cortex.

SUMMARY

The adrenal tissue in cats was reduced by cautery together in some instances with removal of one gland.

Seven of 17 animals in which both medullae were destroyed (uncomplicated with infections) died in all but two cases several weeks after the operation. Lipoid was usually present in the cortex which had been re-

duced considerably. Small numbers of medullary cells were often present. The remaining 10 cats were killed after several months. These seemed to have more active cortex.

Fourteen cats with one adrenal removed and the medulla of the other cauterized, died within a few weeks or months.

All cats (six) in which the cortices alone of both adrenals were destroyed, to about the same extent as when the medullae were cauterized, survived. This may have been due to less injury to cortical tissue indirectly through interference with the blood supply.

Hypertrophy of the remaining adrenal tissue could not be demonstrated beyond question.

These experiments indicate that it is possible to produce chronic adrenal insufficiency by extensive cauterization. They also suggest that destruction of too much tissue may prevent hypertrophy.

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DIAGNOSIS AND TREATMENT OF HYPOGONADISM IN THE MALE*

E. PERRY McCULLAGH, M.D.
D. ROY McCULLAGH, Ph.D.
AND
N. FRED HICKEN, M.D.
Cleveland Clinic
CLEVELAND, OHIO

INTRODUCTION

This study of the problem of hypogonadism in the male is presented chiefly from a clinical point of view. The physiologic and biochemical work has been carried on under the direction of D. Roy McCullagh and has been done with a two-fold aim: (1) the development of the methods for production of large quantities of testicular hormone in a suitable form for clinical use, and (2) the development of laboratory methods for the diagnosis of insufficiency of this hormone in patients.

Previously there were three reasons why men with hypogonadism should not be treated: (1) There was an insufficient amount of the hormone available for clinical use; (2) some preparations containing the hormone have been shown to cause testicular damage in animals (1), and (3) there was no good method for the clinical diagnosis of hypogonadism in the male. We believe that none of these reasons is now valid.

The hormonal preparations employed in these physiologic and clinical investigations have been made by the extraction of male urine. The question naturally arises as to whether or not the treatment of hypogonadism by the methods described is actually a replacement therapy. There is very good reason to believe that the comb-growth-promoting substance which is found in the urine of men is elaborated in the testes. The extracts prepared from the urine have identical physical, chemical and physiologic properties, (2) with those obtained from the testes. A comb-growth-promoting substance can be extracted from the blood, urine or spinal fluid of normal men but is not demonstrable in the body fluids of eunuchs.

A TECHNIQUE FOR THE STUDY OF TESTICULAR ACTIVITY

The exocrine activities of the testes are not a reliable measure of the endocrine functions of the glands. For example, cryptorchidism will inhibit spermatogenesis without preventing the production of the hormone which maintains the structure and function of the prostate. It has become necessary for research and diagnostic purposes, to devise a method for the study of the amount of this hormone produced. The testes produce a substance called androtin (3), which causes comb growth in the caponized

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roosters, and which is responsible for the development and maintenance of most of the unique attributes of the male.

THE PREPARATION OF TESTICULAR HORMONE FOR CLINICAL USE

The testicle is so constructed that it is impossible for any large quantity of the hormone to be stored in the gland. It is therefore not practicable to recover enough hormone from the gland for extensive clinical use. The hormone has been investigated from a chemical point of view by Butenandt (4), and according to him, its empirical formula is $C_{18}H_{26}O_2$, and the molecule is so small that a relatively large quantity escapes through the kidneys and appears in the urine, which is the best source for the preparation of large quantities of the hormone. The method of extraction used is one based on the findings of Dodds and his collaborators (5).

There is no satisfactory chemical test for androtin. However, the substance is very active physiologically, and several methods of biologic assay have been devised. Moore (6) and his collaborators have discussed these methods in detail. For clinical purposes we have found the most suitable test to be that based on the property possessed by the hormone of causing comb growth in capons. The test as employed by Gallagher and Koch (7) and also by Funk (8, 10) is not very suitable for use in men because of the amount of time and material required. To make the test of clinical value it has been necessary to use fewer birds and to decrease the period over which the injections of the hormone are made. Although this decreases the accuracy of the assay somewhat, the test as outlined below gives valuable clinical information.

The Technique of Caponizing. It is not uncommon for workers inexperienced in the technique to encounter considerable difficulty in their first attempts at caponizing. A brief description of the process is here given. A more detailed account is given by Ward (9).

The most satisfactory birds are brown Leghorns, white Leghorns, or black and red Bantams. There is no appreciable difference in the sensitivity of these birds to the hormone. Plymouth Rocks are definitely less sensitive. The surgical procedures are easiest if the cockerel is two to four months old, but if care is exercised it is quite possible to operate on birds of any age. The caponizing of adult bantams is the most rapid method of producing birds suitable for these tests.

The birds should not be allowed to have food or water for at least 24 hours before the operation. Poultry farmers and veterinarians in caponizing use no local or general anesthetic and no aseptic or antiseptic precautions. Before being placed on the operating table the birds are plucked over a considerable area around the last rib on both sides. Both glands can be taken out from the same approach, but it usually is simpler to operate first on one side and then on the other.

The legs are bound together and the wings are tied close to the shoulders. The bird is then extended on its side by hooking weights on the

ties and permitting the weights to hang over the side of the table. The skin is made taut by pulling it anteriorly. The incision, about 2 cm. in length, is made on a line parallel to and directly over the last rib. When the skin returns to its normal position, the incision lies over the muscles of the thigh. Almost immediately above the last rib, the anterior margin of the maximus primus appears. This muscle is retracted posteriorly, and the last intercostal space is opened by puncturing with a small hemostat about 1 cm. from the point where the rib becomes superficial. This aperture is enlarged by spreading the jaws of the hemostat. The ribs are retracted with a permanent retractor. Frequently if the retraction is very strong a rib breaks; this is an inconsequential accident. The peritoneum can be opened with a small sharpened hook. The testis lies adjacent to the great vessels immediately anterior to the kidney. It appears as an ovoid yellowish structure which varies greatly in size in young birds of the same age and weight.

In a young bird the gland has a loose pedicle. A snare, such as that illustrated in the diagram (Fig. 1) is slipped over the gland and is ad-

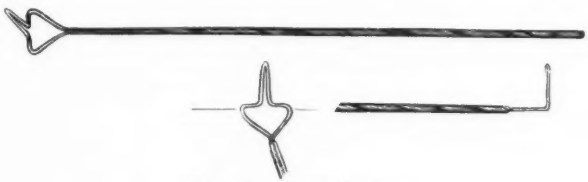

Figure 1. Caponizing snare.

justed so that the pedicle engages in the small part of the loop. When the snare is lifted and rotated, the pedicle usually breaks, and there is very little hemorrhage if the structure has been sufficiently twisted. If the pedicle withstands considerable traction it is crushed with a hemostat and cut. During this stage of the operation care should be taken not to rupture the thin-walled vena cava or the large vessels in the region of the kidney.

In the adult cock the pedicle is very short and firm and completely concealed by the large gland. A ligature is placed around the pedicle with an aneurysm needle. The ligature is tied firmly and gentle traction applied to it so that a small curved hemostat can be passed posterior to the gland to clamp the pedicle. The gland is removed. The pedicle contains several large short vessels which must be ligated carefully behind the hemostat.

The intercostal space is closed by passing a silk ligature around both adjacent ribs. The gluteal muscles cover this incision. The skin incision is closed with one or two silk sutures. Many operators use no ligatures or sutures on young birds. However, these precautions must be taken in adult birds, and we use them consistently for they completely prevent both

young and old birds from becoming "wind puffed." If the birds should become "wind puffed" after the operation, the skin should be incised and the air liberated, or the bird may die. The bird should receive nothing but bread and milk for 24 hours after the operation.

The Extraction of the Hormone. In preparing the hormone from urine, spinal fluid, or blood for assay no attempt at purification is made. The object is to concentrate the hormone by a standard technique until it is in a convenient form for injecting into the capons.

Urine. A 48-hour specimen of urine is acidified with hydrochloric acid. Usually 50 cc. of concentrated hydrochloric acid are sufficient, unless the urine is very alkaline. It is essential that enough acid be added to dissolve all the phosphates. Chloroform is added in the amount of 333 cc. per liter of urine, and the whole is boiled on a water bath under a reflux condenser for eight hours. A small stream of air is passed into the chloroform to prevent bumping. This procedure is almost identical with that of Funk, Harrow, and Lejwa (8, 10). At the end of the eight-hour period the chloroform is separated from the urine by means of a separatory funnel, and is recovered by distillation. The residue in the distilling flask is removed with ether to a small beaker. The ether is removed by evaporation in a current of air, and the residue dissolved in 4 cc. of sesame oil, using two washings of 2 cc. each.

We have found that the efficiency of this method is only about 50 per cent, but we have not thought it worth while for the present to change the procedure, since this gives comparable results in all cases. Six liters of urine were extracted by this procedure and the extract was injected into four birds by the usual assay method, giving a growth of 7 mm., 4 mm., 4 mm., and 3 mm. That represents the amount of hormone that we have been extracting. However, after the same urine was re-extracted a second time and then injected into two birds it gave 8 mm. of comb growth in one bird and in another a growth of 3 mm. The total extract from a third extraction was injected into one bird with a resulting comb growth of 5 mm. The fourth extraction when injected produced no comb growth at all.

Spinal Fluid. Spinal fluid is treated in exactly the same manner as urine. If possible, it is usually best to obtain 100 cc. of spinal fluid; the material extracted by chloroform is taken up in 4 cc. of sesame oil.

Blood. Oxalated blood (50 cc.) is mixed with 50 to 75 gm. of anhydrous sodium sulphate. This method of desiccation has been used by Frank and Goldberger (11) in their procedure for the extraction of theelin from the blood. They advise continuous stirring until the mixture forms a dry powder. The extraction can be made with greater ease if it is commenced when a very thick, heavy sludge is formed. Sufficient sulphate is added to bring about the formation of this pasty sludge, which is extracted three times with 200 cc. of ether. On the first addition of ether

the mixture forms a fine suspension in the solvent. Each washing with ether is left in contact with the blood, and occasionally stirred for at least half an hour before being removed by decantation. A certain amount of the combined ether washings must be centrifugalized in order to remove the last of the suspended material. The ether is recovered by distillation and the residue is taken up in sesame oil in the same way as is the material obtained from urine and spinal fluid.

We believe that extraction of blood gives almost 100 per cent yield of hormone. Further extractions have been made on samples of blood which produced no further comb-growth in the capons.

The Assay. When studying normal persons, the quantities of blood, urine, and spinal fluid just indicated, yield in each case sufficient hormone to permit the use of two birds for the assay. In patients, in whom a deficiency of the hormone is suspected, urine and blood are assayed so that at least four birds are used for a single test. The capons should be kept in a well-lighted, well-ventilated room at a temperature of about 18° C. Only adult birds with combs in a state of complete regression are used. Each bird receives 1 cc. of the extract, prepared as described, daily, for two consecutive days. The injections are made deep into the pectoral muscles. The difficulties encountered in injecting such a heavy oily preparation are greatly diminished if the oil is kept in a warm place. The hormone is very thermostable and is not destroyed, even though the oil be brought to the boiling point. It is unnecessary to sterilize the preparations since the birds are very resistant to infections.

The length and height of the comb are measured in millimeters. In each case definite anatomic points must be selected for measurement, but this presents no difficulty.

To obtain comparable results, the points chosen should represent as nearly the maximum length and height as possible. The total growth (the sum of the increase in length and in height) is the index used to determine the activity of the preparations. Sometimes testicular rests will suddenly proliferate and become active. Hence, unless the growth of the comb, following injection of the hormone, is succeeded by regression, the effect is not considered to be due to the hormone.

When using material from females, preadolescent males, or men suspected of hypogonadism, twice the amount of extract should be injected into the capons. This necessitates using twice as much blood, urine, or spinal fluid, or using only one bird instead of two in the assay of each lot. With normal men, the assay can easily be varied in accordance with the amount of material obtained.

The results of a typical test are given in the accompanying table (Table I). The blood, urine, and spinal fluid all were obtained from the same patient.

During the course of the research about 50,000 bird units have been prepared by this method.

TABLE I

	Urine	Blood	Spinal Fluid
Total amount extracted	48 hour specimen	50 c.c.	50 c.c.
Total comb growth	1st bird, 4 mm. 2nd bird, 6 mm.	1st bird, 2 mm. 2nd bird, 3 mm.	1st bird, 2 mm. 2nd bird, 3 mm.

The preparations used for clinical purposes have been assayed by the methods described above. In order to increase the accuracy of the assay, at least five capons have been used in all such tests.

TOXICITY

The question of possible testicular damage caused by injection of this hormone is of importance. Normal adult male rats have been given 18 units of this material per day for six weeks and no testicular damage could be detected. Further experiments of this type are under way but to date there is no evidence that this preparation causes damage to the testes. It should be borne in mind that the preparations shown to have caused testicular damage were made from testes and contained a very different set of impurities from the material used here. If doses of 18 units per day do not cause testicular damage in rats, it seems unreasonable to suppose that 6 units every second day would do so in man.

The preparation used clinically has been injected repeatedly into capons over a period of a year and a half and the birds have remained in good health. Rats receiving doses as high as 18 units per day for six weeks have remained in good health.

Clinically there is no local or general reaction to its use, except occasionally slight malaise after the first injection, but this has been absent subsequently.

CLINICAL RESULTS

In touching upon the clinical aspects of this problem, no attempt will be made to review previously accumulated clinical data relating to diagnosis. Observations on the problem will be presented by citing some of the cases which have come to our attention in which a deficiency of the hormone could be demonstrated in blood and urine. An attempt has been made to correlate the symptoms and clinical findings with this known deficiency and to present the observations on the effects of specific therapy in some of these cases. Cases of hypogonadism considered to be complicated by pituitary deficiency in boys are not included in this report.

The diagnosis of hypogonadism in castrates is obvious. We have observed eight such cases in adult males.

Case I. A Jew, 36 years of age, was seen in September, 1930. About two and one-half years before he had had a unilateral orchidectomy and a little more than a year later the remaining testicle had been removed on account of tuberculous orchitis. At the time of his first operation he weighed 140 pounds and there were no signs of pulmonary disease. After the first operation he had

felt well, had worked, had gained weight and had had normal libido, with sexual intercourse about twice weekly. After the second operation he had normal intercourse twice within two months. Since then he had not experienced any libido, and had had no erections or nocturnal emissions. The penis had become much smaller since operation.

In spite of much loss of sleep and limited diet his weight had increased to 165 pounds when he came to the Clinic. The fat was distributed chiefly in the region of the abdomen, hips and breasts. He had noted no change in the growth of his beard. The patient reported that the growth of hair on his body had always been scant. His body was practically hairless except for scanty axillary and pubic hair, the distribution being of the feminine type. Very small sparse hairs were noted on the arms and legs; the growth of hair on the head appeared normal. The patient had noticed that his skin had become finer in texture, and slightly pale, but it was normally moist. He had become very nervous and excitable; severe hot flashes, accompanied by sweats had occurred many times each day. He felt weak and tired constantly. He complained of headaches and dizziness and occasional fainting spells. These symptoms no doubt were aggravated by much loss of sleep and the nervous trauma incident to the increasing pain in the perineum, groins and back, which was due to tuberculous prostatitis and seminal vesiculitis. He had developed no paresthesia, and there was no dryness of the hair or nails. There was no edema or other striking signs of hypothyroidism. The patient seemed dull, somewhat apprehensive, and answered questions slowly.

The pulse rate was 76, blood pressure 134 systolic, 80 diastolic. The thyroid was not enlarged. The prostate was very hard, tender and its size was about one-fifth that of a normal gland; no fluid could be expressed from the prostate. The scrotum was empty and the penis very small.

Repeated assays of blood, urine and spinal fluid showed no evidence of the presence of the male sex hormone. Roentgenograms of the chest and of the sella turcica revealed no demonstrable lesion or abnormality. The basal metabolic rate was minus 19 per cent. The blood count was normal and repeated checks have shown no monocytosis, lymphocytosis or other abnormality. Except for the occasional presence of acid-fast bacilli, urinalyses yielded normal findings. There was an increased amount of cholesterol in the blood. The Friedman test was made twice with the same results on each occasion. The patient's urine (24 cc.) was injected intravenously in divided doses into a rabbit isolated for three weeks. Forty-eight hours later there was marked redness of the uterine horns, many follicles and young corpora lutea were present and ovulation had occurred. There were no hemorrhagic follicles. From this, overproduction of anterior pituitary sex hormones may reasonably be assumed. Other interesting laboratory data are included in the accompany table (Table II).

TABLE II

CASE I

Before Treatment					After Ttreatment			
B. M. R.	Blood Chemistry			Glucose Tolerance		B.M.R.	Blood Chemistry	
9–9–30		4–27 (1931)	8–25		Androtin			
—15%				F 86	6 units	10–29–31		
8–25–31	Sugar	76.	101.	½ hr. 152	Q. D. 6	—1%	Sugar	97.
—19%	Urea	36.	33.	1 hr. 124	days		Urea	45.
	Uric acid	2.4	1.9	2 hr. 130	per	11–4–31	Uric acid	1.7
	Creatinin	1.3	1.1	3 hr. 87	week	—5%	Creatinin	1.2
	N. P. N.	22.4		4 hr. 75	from		N. P. N.	33.6
	Chlorides	577.	577.		8–28–31		Chlorides	544.
	Calcium	11.1	11.1		to		Calcium	
	Phosphate	3.6	3.6		11–9–31		Phosphate	
	Cholesterol	400.	384.				Cholesterol	285.
	Protein	7.4	7.8				Protein	6.5
	Albumin	3.5	4.0				Albumin	3.2
	Globulin	3.9	3.8				Globulin	3.3
No treatment for two months.								
—17%	Cholesterol	384			6 u. q. 2nd day, 2 weeks	—16%	Cholesterol	272

Treatment was carried on intermittently between October, 1930, and December, 1930, and was discontinued only because sufficient hormone was not available. Between August 28, 1931, and November 9, 1931, the patient received 6 bird units in 1 cc. of oil intramuscularly six days per week.

As the result of this course of treatment the patient became less nervous and slept better, the dizziness and weakness decreased, and the hot flashes were definitely diminished but did not disappear entirely. He felt much better subjectively and wished to continue treatment. There was no decrease in his weight or increase in growth of hair during this time. The prostate showed a questionable increase in size.

Figure 2 shows the rate of excretion of androtin in this man. Two assays immediately preceding treatment showed absence of the hormone in the urine.

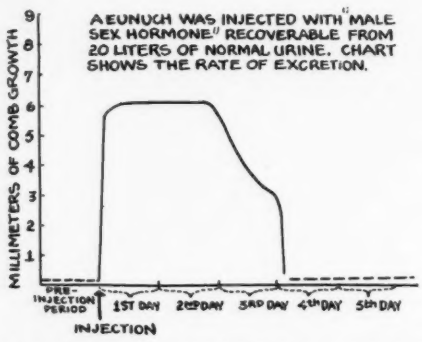

Figure 2. Rate of excretion of male sex hormone in a eunuch receiving extract from normal urine.

Twenty-four bird units were injected in one dose and the comb-growth obtained from extracts made from twenty-four specimens on the following days are indicated. On the fourth day following injection no hormone could be detected in the urine.

Treatment has been given intermittently since then and at present he is being given 6 bird units three times per week. Asthenia and fatigue still are present, but may be ascribed partially to the fact that he gets only three to four hours' sleep each night on account of severe pelvic pain.

Case II. A married man, aged 33, had had a bilateral orchidectomy for tuberculous orchitis in 1925. Following this operation, symptoms and signs of pulmonary tuberculosis had developed but since 1929 no signs of activity of the pulmonary disease had been present. After the operation libido was greatly diminished but potence, although diminished, persisted and he had been capable of intercourse every two to three weeks. He had a normal orgasm except that he believed that ejaculation did not occur. There had been considerable atrophy of the penis. A short time after his operation he began to have severe hot flashes associated with nervousness and sweating and fatigue; these occurred several times daily. The hair on his head seemed normal and the beard showed a questionable retardation of growth. He said that previously his limbs and trunk were hairy, but within a year after his operation his body hair had almost completely disappeared, except for a few short hairs about the nipples, sparse axillary and scant pubic hair which had assumed a feminine type of distribution. The skin had become fine in texture and his complexion sallow. Before 1925 he weighed about 150 pounds. Since the onset of tuberculosis he had gained weight steadily; in March, 1932, he weighed 174 pounds. The increased fat was distributed chiefly about the breasts, abdomen and hips.

Examination revealed a bright looking young man, whose skin was sallow, dry, of fine texture and showed very fine peculiar wrinkles. The examination of the chest showed no signs of tuberculous activity. He had a palpable diffuse goiter. The prostate was one-fourth to one-fifth normal size and was flat and solid, but not hard. It was not tender, and vigorous prostatic massage failed to produce any secretion.

The pulse rate was 80, temperature 98.6° Fahrenheit and the blood pressure, 120 systolic, 72 diastolic. A roentgenogram of the chest showed signs of old pulmonary tuberculosis. Radiographic examination of the sella turcica showed nothing abnormal. The visual fields were normal. The basal metabolic rate was minus 16 per cent. Urinalysis, blood counts and Wassermann tests were normal. There was increased glucose tolerance. Blood sugar estimations, fasting and following the administration of 100 grams of glucose orally at one-half, one, two, three and four-hour intervals were 80, 116, 98, 82, 65, 75. The chemical analysis of the blood, including determination of urea, uric acid, creatinin, non-protein nitrogen, chlorides, calcium, phosphorus, cholesterol, proteins, albumen, and globulin gave normal findings except for a high cholesterol value, 250 mgm. per cent.

The Friedman test was positive, showing ripe follicles, ovulation, and corpora lutea hemorrhagica. The assay of blood and urine failed to reveal the presence of any male sex hormone.

Treatment was begun March 4, 1932, with 6 bird units of androtin every third day. The patient noted an increase in energy, which was the first sign of change. The nervousness disappeared, but the hot flashes, although diminished, persisted in very mild form. After about a month of treatment there was a marked increase in libido and potence and sexual dreams occurred. The color of the skin improved.

On April 29, 1932, no change could be detected in the size of the prostate, or in the amount or distribution of hair. His weight was 175 pounds. The basal metabolic rate, on this date, was still minus 16 per cent. The only definite change in blood chemistry was a reduction in blood cholesterol to 184 mgm. per cent.

The other six eunuchs examined will not be reported in detail here. The following table gives some indication of the signs and symptoms in this group. (Table III.)

TABLE III

REPORT OF 8 CASES OF EUNUCHISM

	AK	CM	NT	DE	AN	AR	HM	OS
Age	36	33	61	50	54	51	65	47
Duration (years)	21½	7	5	27	14	1	½	½
Impotence	+	+*	+*	+	+	+	+	+
Diminished libido	+	+	+	+	+	+	+	+
Diminished energy	+	+	+	0	0	0	+	0
Nervousness	+	+	+	+	+	+	0	0
Hot flashes	+	+	+	0	+	?	+	0
Atrophied prostate	+	+	+	+	+	+	op.	+
Atrophied penis	+	+	op.	0	0	0	?	0
Hypotrichosis of the body	+	+	+	+	+	+	0	+
Hypotrichosis of the face	0	?	+	+	+	+	0	0
Skin change	+	+	+	+	+	+	+	+
Weight gain	25	24	27	?	15	+	25	20
Abnormal distribution of fat	+	+	+	0	+	0	+	+
Testis hormone in urine	0	0	.....	0	0	0	0	0
Testis hormone in blood	0	0	0	0	0	0	0	0
Testis hormone in cerebro-spinal fluid	0	.....	.....	.....	.....	.....	.....	.....
Friedman test	±	+	.....	+	+	.....	.....	0
Abnormal sella	0	0	0	0	0	.....	0	0
Increased glucose tolerance	0	+	Sugar 179	0	0	.....	Diabetic	0
B. M. R.	−19	−16	.....	−15	−18	.....	+5	−7
Calcium	11.4	10.9	9.7	10.9	11.4	.....	10.4	.....
Phosphate	3.2	3.4	.....	4.2	4.2	.....	4.3	.....
Cholestrol	400	250	155	159	272	.....	187	187

*Partial impotence.

It is interesting to note that libido and potency were diminished in every case, although impotence was only partial in two of the cases. The presence of atrophic changes in the skin was a constant feature in this group, the skin being of very fine texture, finely wrinkled and of a sallow color. A gain in weight occurred in seven of the cases and it is possible that some gain in weight could have occurred in the other case and have been forgotten by the patient inasmuch as twenty-seven years had elapsed since orchidectomy.

The results of the Friedman test appear to indicate a definite tendency to pituitary hyperfunction in this group. In the first case, many follicles appeared,

ovulation had taken place and fresh corpora lutea were present, but no hemorrhagic follicles appeared. In the second case, all three phenomena occurred and in the third case, ovulation had taken place and although no fresh corpora lutea were present, hemorrhagic follicles were seen.

It is interesting also that in every case in which it was measured there was a definite decrease in the metabolic rate of all these patients, except those castrated within six months.

The following cases are examples of hypogonadism in the adult male. They belong to a group of 19 patients who have been treated within the past year and a half. All of these men presented suggestive symptoms and signs of gonadal hypofunction, and a deficiency of the male sex hormone was demonstrated in the blood or urine in all cases. A few of these have received treatment much of the time since October, 1930, and some for only a few weeks. Rather than try to draw general conclusions from an analysis of a small group, actual findings are presented in a few cases.

Case III. A man, aged 29, single, complaining of impotence and nervousness first was seen September 4, 1931. He had had nocturnal enuresis until he was 14 years old. The patient said that he has three brothers, all of whom have moderately hairy bodies, but the patient had very little hair on his trunk. In his brothers, puberty had appeared when they were 13 to 14 years of age; in the patient at the age of 17. His voice is higher than his brothers'; they shave daily, and he shaves only every second or third day. For the past five years erections had been noted only once every second or third month and there had been none for six months prior to examination. Nocturnal emissions never had occurred more than once in five or six months. No other symptoms suggestive of pituitary or other disease were elicited.

Examination revealed a healthy looking male, 66 inches in height, weighing 144 pounds. The skeleton and skin appeared essentially normal. The hair was sparsely distributed on the body but pubic hair was normal in distribution. The penis and testes seemed normal in appearance and on palpation. The prostate was normal in size; its secretion was plentiful, containing a few pus cells, and many lecithin bodies, but no sperms were seen. The roentgenogram showed the sella turcica to be normal. The blood Wassermann test was negative. The chemical analysis of the blood gave normal findings except for an increased level of cholesterol, 200 mgm. per cent. The glucose tolerance was slightly increased after 100 grams glucose by mouth. Blood sugar determinations made at one-half, one, two, three, and four-hour intervals gave the following values in mgm. per cent: 100, 141, 113, 116, and 94. The basal metabolic rate was minus 9 per cent. The assay of blood and urine for male sex hormone revealed only 3 mm. comb growth in each of two reliable birds in spite of the fact that each bird received the extract from a forty-eight-hour specimen of urine, which is approximately normal for extracts from half the amount of body fluids.

Treatment. Between September 9, 1931, and October 8, 1931, he received 6 bird units of androtin in oil daily. His weight remained stationary, his nervousness diminished very little, but from September 25th he noted erections daily. From October 8 to 13 he received injections of aqueous solution, which was shown later to be inactive, and during this time one erection occurred. October 13 to October 22 he received 1 cc. of androtin a day. Between these dates erections occurred daily. Nocturnal emissions occurred four times. His nervousness persisted and no other changes were noted. On October 22, the basal metabolic rate was plus 26 per cent and the glucose tolerance curve was normal. No change could be detected in the prostate and no spermatozoa were seen in the prostatic secretion.

Between October 22 and December 28 no treatment was given. Erections appeared daily and nocturnal emissions about once in ten days. On November 18 the basal metabolic rate was minus 8 per cent and blood chemical findings were practically the same as on admission. The blood cholesterol was still high. 214 mgm. per cent. During this time no change in the size or the amount of secretion from the prostate was noted. December 28, the administration of twelve units of androtin every second day was commenced and continued until January 28. On December 30 the basal metabolic rate was minus 9 per cent.

On January 22, 1932, the prostate was thought to be larger; the secretion was profuse, contained much lecithin, an occasional pus cell, many dead sperms and a moderate number of actively motile ones. This was the first time spermatozoa had been seen in fluid obtained by prostatic massage.

The outstanding results of treatment appeared to be marked increase in potency and increase in the basal metabolic rate. The fact that after repeated

prostatic examinations, sperms were found only after treatment may or may not be significant. There was little effect on the nervous symptoms and no change in weight occurred.

Case IV. A man, aged 35, single, came to the Clinic, October 6, 1931, with the complaints of impotence, fatigue and nervousness. He had developed normally except that the left testis had been in the groin until it was brought down to the scrotum by operation when he was 14 years of age. Puberty had been normal. Libido was normal and between the ages of 19 and 23 he had had normal intercourse frequently and had felt well generally.

In 1919 libido and potency had gradually diminished and disappeared. Since that time he remembered having only one erection. During the past five years especially he had felt fatigued and weak, somewhat drowsy and depressed. He also had had frequent spells of dizziness in which he felt that the blood rushed to the head. The most annoying symptom had been the lack of energy.

There has been no gain in weight, or change in the distribution of hair. There were no symptoms suggestive of pulmonary or thyroid disease.

Physical examination showed that his height was 64 inches, and his weight 140 pounds. The temperature was 98.6° F.; the pulse rate, 68; the blood pressure, 110 systolic, 80 diastolic. There was no evidence of goiter, and the general physical findings were essentially normal except for slight atrophy of the left testis. The penis was normal, the prostate was of normal size and consistency and the prostatic fluid contained a few prostatic cells, no white blood cells, and a few non-motile spermatozoa.

Special examinations of the eyes, of the nose and throat and of the vestibular apparatus and complete neurologic examination gave normal findings. Roentgenographic examination of the skull revealed an abnormally large sella turcica. An encephalogram ruled out the possibility of the presence of a pituitary tumor. Urinalyses, blood counts, and blood Wassermann were normal. The basal metabolic rate was minus 13 per cent. Assay of the blood for male sex hormone revealed none.

The glucose tolerance was normal and the blood cholesterol was 187 mgm. per cent.

Treatment. A factor of pituitary deficiency was suspected and the patient was given the gonad-stimulating hormone from pregnancy urine in the form of Antuitrin-S, 100 units per day for six days a week, from October 19 to November 20. During this time he noted some increase in strength and bodily vigor but no increase in potency. Examination of the prostate showed no changes; no sperms were noted. The basal metabolic rate was still low, minus 16 per cent.

November 31, 1931, the administration of Antuitrin-S was discontinued and male sex hormone in the form of androtin, 12 bird units in 2 cc. of oil, was given three times per week until December 31. On December 3 an erection occurred, the second experience in twelve years, this recurred on the 8th and from December 14, partial or complete erections occurred almost daily. Several nocturnal emissions also occurred. Bodily vigor was markedly increased, the dizziness and flashes of heat disappeared, and the patient felt better than for many years. On December 14 a few slightly motile sperms were seen in the prostatic smear.

Since January 1 the dose has been reduced to 6 bird units twice a week and on January 22 many actively motile sperms were found in fluid obtained by prostatic massage. At the present time the patient is relieved of all his symptoms.

On April 8, 1932, the basal metabolic rate had risen to minus 5 per cent and the cholesterol had decreased to 167 mgm. per hundred cubic centimeters of blood. Other laboratory examinations showed completely normal findings.

Case V. On May 15, 1931, a single man, 35 years of age, came to the Clinic because his sexual potency had been diminishing for two years and had been completely absent for six months. Libido was still present but greatly diminished. For several months he had had hot flashes three or four times each week. He complained of feeling dull and of having no energy. During the last two years he had gained 40 pounds in weight, much of it about the abdomen. The hair on his head and his beard remained normal, but the hair on the trunk had become sparse. He had had gradually increasing generalized headaches for two years.

He was a stout man of dull appearance. His height was 62 inches and his weight 164 pounds. The breasts were large and the abdomen protuberant. There was no hair on the trunk except a few sparse hairs about the nipples, a

few sparse axillary hairs and a female escutcheon of pubic hair. The skin was fine and slightly pale. The thyroid gland was not enlarged. The penis was small, the testes normal to palpation and the prostate seemed normal in size and consistency. The prostatic secretion was plentiful with much lecithin and one to five pus cells per high power field, but no spermatozoa were seen. Visual fields and ophthalmoscopic examination showed no abnormality. Roentgenographic examination showed that the size of the sella turcica was increased, but the roentgenologists did not believe that this indicated the presence of a tumor. The blood pressure was 100 systolic, 72 diastolic. The basal metabolic rate was minus 12 per cent. Urinalysis, blood counts, and the blood Wassermann test yielded normal findings. The glucose tolerance was slightly abnormal, showing the following: fasting, 71; one-half hour, 176; one hour, 267; two hours, 252; three hours, 91; and four hours, 61. The level of cholesterol in the blood was 180 mgm. per cent. Other chemical tests of the blood showed normal values. The Friedman test indicated the presence of the gonad stimulating hormone. An assay of the blood and urine showed that the amount of testicular hormone was decreased. Extracts of the blood gave no growth on two tests, but 3 mm. growth was produced by extract from a 24-hour specimen of urine on one occasion, none on another.

Treatment. Between March 18 and April 9, the patient received androtin (6 units in 1 cc. of oil) every second day with no noticeable improvement. On April 9 the headache was improved and the patient felt more energetic and noted a partial erection. From this date until April 22 he received 12 units twice each week. On April 19 the patient was euphoric, and said that he felt strong, energetic and warmer than before this treatment was started. The hot flashes had disappeared, the headaches had diminished, and an erection appeared almost daily and at times was complete. Nocturnal emissions had occurred twice. However, the prostate showed no change and examination of a prostatic smear showed no sperms.

The basal metabolic rate was minus 11 per cent on April 23, and a second test gave the same result. On May 4, the basal metabolic rate was minus 1 per cent and on a second test, minus 5 per cent. The glucose tolerance curve was as follows: fasting, 90; one-half hour, 175; one hour, 248; two hours, 200; three hours, 78; and four hours, 75. There was essentially no change in the chemical findings in the blood.

Case VI. A man, aged 38, married since 1930, had been normal sexually until after repeated bilateral hernia operations in 1928 and 1929. After this he had lost libido and potency and had become less energetic. The growth of his beard was retarded and he had lost much hair from his arms, legs and trunk. He complained also of hot flashes.

The prostate was smaller than average, yielding scant secretion. The sella turcica appeared normal in the roentgenogram. The basal metabolic rate was minus 10 per cent. The blood Wassermann was negative. The glucose tolerance curve, urinalysis and blood chemical analyses were normal except for the amount of cholesterol which was 353 mgm. per cent. The assay of the blood and urine indicated a deficiency of the testicular hormone.

Treatment with androtin, 1 cc. (6 bird units) every second day was begun on February 16, 1932. On March 4, a nocturnal emission occurred for the first time since 1928. On March 5, normal intercourse was accomplished for the first time since marriage. The patient's energy has increased and sexual potency has persisted.

Case V. A married man, aged 35, consulted us because of sudden nocturnal attacks of nervousness, extreme sense of heat and palpitation, followed by profuse perspiration. These attacks occurred almost every night and led to considerable loss of sleep. For two years libido and potence had diminished. There was no history of testicular injury and there had been no change in weight or in the growth of the hair. There were no other symptoms suggesting thyroid or pituitary disorder.

The basal metabolic rate was plus 3 per cent. The levels of urea, uric acid, creatinin, calcium, phosphorus, cholesterol, and serum proteins in the blood were normal. Radiographic examination of the sella turcica showed no abnormality. The assay of the blood for testicular hormone showed 1 mm. growth in each of two birds, and of the urine gave no growth in either of two birds.

During the two months of treatment with 6 units of androtin every third day attacks of heat and palpitation occurred infrequently at first and not at all for one month. Potency has increased slightly.

Case VI. An unmarried man, aged 44, had had a severe Neisserian infection when he was 20, which had produced a chronic prostatitis and posterior urethritis requiring treatment. Libido and potency had been normal until he was about 37. For five years impotence had increased steadily and for one year sexual activity had been possible only at intervals of one or two months. For two years he had had sudden flashes of heat accompanied by nervousness and perspiration several times daily. He had noted no gain in weight, change in the distribution of hair, or atrophy of the penis or prostate. The roentgenogram of the skull showed no change in the sella turcica. The basal metabolic rate was minus 4 per cent. Blood counts, urinalysis and the values for uric acid, creatinin, non-protein nitrogen, chlorides, calcium, phosphorous and serum proteins in the blood were normal. Tolerance for glucose was slightly increased: fasting, 98; one-half hour, 133; one hour, 118; two hours, 84; three hours, 78; four hours, 68. Assay for testicular hormone showed it to be absent in blood and urine on one occasion, but was present in the urine on a second test.

Treatment consisted of 6 units of androtin three times weekly during one month, which resulted in a marked reduction in hot flashes and nervousness and a questionable increase in potence.

Case VII. A married man, aged 35, for nine years had had gradually increasing impotence, accompanied by loss of energy and strength. This had worried him considerably.

The penis and testes appeared normal; the prostate was small and firm, and the prostatic secretion was very difficult to obtain, but on examination was normal. The uninalysis and blood counts were normal. The Wassermann test was negative. The sella turcica appeared normal in the roentgenogram. The basal metabolic rate was minus 9 per cent. There was increased glucose tolerance: fasting, 77; one-half hour, 104; one hour, 84; two hours, 57; three hours, 56 and four hours, 46. Assay of the blood and urine for testicular hormone was not made. However, the patient was given a course of treatment with androtin. He has not returned to the Clinic, but a letter from his physician, written on November 17, 1931, stated: "He has had sixteen injections, 1 cc. each, and feels much better. He is more alert, more active and is not half as depressed as he was. He had been worrying for a long time about his impotency." And on March 28, 1932, a second note from his physician said that he had progressed nicely for five months but was having a little difficulty and would like to have a further supply of the extract.

COMMENT

The above cases serve to demonstrate the type of case in which a diagnosis of hypogonadism has been reached and some of the effects of treatment to date. Androtin was the only medication used except in the case cited in which preliminary treatment with Antuitrin-S. was administered. Some degree of improvement has been noted in all cases in which there were suggestive signs and symptoms together with a measurable deficiency of the hormone. The patients with the milder deficiencies have seemed to receive the greatest symptomatic benefit, some being entirely symptom-free after treatment. In cases in which no gonadal insufficiency was demonstrated or in which a deficiency was known not to exist, the results of treatment with androtin have been indefinite or negative.

The method of assay has been found useful in determining those cases in which gonadal deficiency was not a factor in the production of symptoms. In one such case impotence had followed resection of the rectum for carcinoma, in another it had followed cordotomy which had been performed for intractable pain. In both cases normal testicular activity was demonstrated.

Four patients were treated because of impotence alone. In two of these no assay was made and in two cases assays revealed a normal amount of the hormone in blood and urine. In two of these patients there was questionable improvement and in two there was no change.

One patient complaining of premature ejaculation was treated without relief. In one patient who was shown to have normal testicular activity, there was sexual perversion accompanied by neurocirculatory asthenia which did not respond to treatment with androtin administered for three weeks.

In one case puberty was not complete at the age of 20 and Froelich's syndrome had been diagnosed at the age of 13. Extracts of 24-hour urine specimens produced a comb growth of 3 and 4 millimeters. A boy, 14 years of age, was suspected of having hypogonadism because he had very few signs of puberty and his body proportions were suggestive, the span being greater than the height. However, his urine contained large amounts of the hormone. In other cases diagnosed clinically as pituitary deficiency, assay of the blood and urine has shown an accompanying gonadal deficiency.

Psychic factors must be kept in mind. In all cases we avoided encouraging the patient so that physiologic changes might be more accurately evaluated. That the psychic factor is extremely important was illustrated by two patients who complained of partial impotence. When these patients were told that they were normal physically and that the blood and urine showed a normal amount of testicular hormone, the impotence disappeared.

SUMMARY

1. The methods and results of assay of 250 specimens of body fluid for testicular hormone by the capon method are outlined.

2. The diagnosis of hypogonadism is discussed by presentation of case histories of two eunuchs and a synopsis of findings in six others.

3. Of a group of 19 cases of hypogonadism treated by standardized testicular hormone (Androtin) the results in seven cases are cited. The most definite demonstrable changes following treatment seem to be a common tendency (1) to a rise in basal metabolism, (2) to a fall in the level of blood cholesterol and (3) to recovery of testicular hormone from the urine after its administration.

In some cases motile spermatozoa have been found in fluid obtained by prostatic massage after treatment, where none were found before.

Common symptomatic changes following treatment have been increase in sexual potence, decrease in vasomotor and nervous disturbances, increase in frequency of nocturnal emissions and increased energy.

4. Types of cases in which the treatment has failed are indicated briefly.

5. The value of the method of assay as an aid in the differential diagnosis of hypogonadism is discussed.

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SOME CHRONIC EFFECTS OF THE ANTERIOR PITUITARY SEX HORMONE ON THE WEIGHTS OF BODY, OVARIES, UTERUS, PITUITARY AND ADRENAL GLANDS

FREDERICK E. EMERY
Department of Physiology, University of Buffalo
BUFFALO

In recent years a great stimulus has been given to research on the problems relating to the physiology of reproduction by the discovery of a hormone in the anterior pituitary gland which acts on the gonads. The original observations of Zondek and Aschheim (1927) and Smith and Engle (1927) gave undisputed evidence of ovarian growth and follicular development in immature and adult rats following pituitary implants. These results have been confirmed in many species of animals by grafts, extracts, urine and blood serum. The positive test in the immature mouse or rat is very definite as seen by enlargement of the ovaries with follicles distended or haemorrhagic, enlarged uterus, vaginal orifice open and cornified cells in the vaginal smears. To obtain this information, the animals are usually sacrificed within a few days after the test is started. The experiments reported in this paper deal with a chronic or delayed effect of the anterior pituitary sex hormones on the weight of the several organs studied.

MATERIALS AND METHODS

The animals used were from a colony of albino rats that have been kept in this laboratory for several years. The donors were for the most part males, castrated when about six weeks old and with an average weight of 175 grams when killed for grafting. Two pituitary glands were implanted in the muscles of 25-day-old recipients weighing 35 to 40 grams on each of two consecutive days. The operation was a modification of that used by Smith and Engle (1927). The tissue was placed in pockets made in the muscles of the hind legs of the recipient rats under ether anaesthesia. Reasonable care was given to sterilization of the instruments and the operative field, as well as obtaining the pituitaries in a sterile manner. The control animals were of the same size, and, when available, litter mates to the grafted animals were used, although this precaution seems to be unnecessary in these experiments. The grafted and control rats were kept in the same cage and fed a ground grain mixture, cod liver oil and green food—a diet we have used in growth and breeding experiments for some time with satisfactory results.

BODY WEIGHT

Several investigators (Wulzen, 1916; Evans, 1924; Putnam, et al., 1928, and Johnson and Sayles, 1929) have shown, beyond doubt, a hor-

mone in the pituitary gland for body growth as demonstrated by feeding hypophyseal substance and also in animals injected with extracts. The experiments reported here were not outlined to bring out the effect of the growth hormone and, therefore, are probably worthy of consideration only in comparison with the recent work of Botchkareff and Preobrajensky (1930). They found that amounts of pituitary extract sufficient to cause marked growth of the sex organs were without effect on the growth of young rats and concluded that their extract did not contain the growth hormone. The data herein also confirm their results on body weight. The experimental animals in this series had been given two castrated male pituitary glands on the 25th and 26th days of age. Without further treatment, these animals were continued under observation for a period of ten months and frequent body weights recorded. The fact that there was no noticeable effect on growth does not mean that the growth hormone was not present. These experiments do clearly show that the amount of implanted pituitary tissue necessary to cause marked growth of the reproductive tract (Table 1) does not cause a noticeable change in body weight.

TABLE 1

Average weights of body in grams; ovaries, uterus, and pituitary gland in milligrams of controls and of rats given implants of two castrated male rat pituitary glands on the 25th and 26th days of age.

Days after last implant +26=age of rats.

Figures represent average of four rats.

Killed Days After Last Implant	Implanted Recipients				Killed Age in Days	Controls			
	Ovaries	Uterus	Pituitary	Body		Ovaries	Uterus	Pituitary	Body
2 days	79	99	3.0	46	28	14.0	34	3.0	47
4 days	110	120	3.0	50	30	15.0	35	3.0	52
8 days	145	160	3.0	60	34	15.0	41	3.0	64
12 days	164	211	3.5	55	38	15.5	40	3.5	58
16 days	115	141	3.8	68	42	16.0	49	3.5	70
20 days	129	263	3.5	91	46	15.5	37	3.9	70
24 days	70	153	4.5	82	50	21.0	93	3.9	77
28 days	70	110	4.4	85	54	18.0	72	3.7	86
36 days	43	100	3.8	78	62	18.0	44	3.8	76
44 days	35	109	3.7	78	70	27.0	65	3.7	79
52 days	52	128	4.8	98	78	25.0	84	4.1	96
60 days	53	100	4.5	128	86	30.0	150	4.8	105
68 days	57	159	6.6	123	94	49.0	255	8.8	128
76 days	48	159	7.0	130	102	42.0	151	7.0	140

WEIGHT OF OVARIES

The changes produced in the ovaries either by pituitary implants (Smith and Engle, 1927), pituitary extract (Evans, 1924; Claus, 1931; Fevol, et al., 1931), the placental preparation as developed by Collip (1930), the pregnant test of urine (Aschheim, 1930), or the blood test of Cole and Hart (1930) are all associated with follicular growth and usually corpora lutea development. Such changes bring about an increase in weight of the ovaries which have been studied in a few cases over long periods in animals treated daily with extracts in connection with body growth experiments (Evans, 1924; Johnson and Sayles, 1929, and Botch-

kareff and Preobrajensky, 1930). The writer has not found any report dealing with the weight of the ovaries many days or weeks following treatment of short duration with the sex hormone of the hypophysis.

The approximate minimal amount of implanted pituitary tissue necessary to excite the sex organs of an immature rat was found to be about one pituitary of an adult male rat. Immature rats thus treated at 25 days of age were in oestrus about four days later, the uterus was enlarged and the ovaries weighed 20 milligrams compared to 15 milligrams for normal untreated rats of the same age The ovaries remained at this weight for a few days and then gradually approached or fell slightly below the weight of the controls (Fig. 1). Although there was no prolonged effect

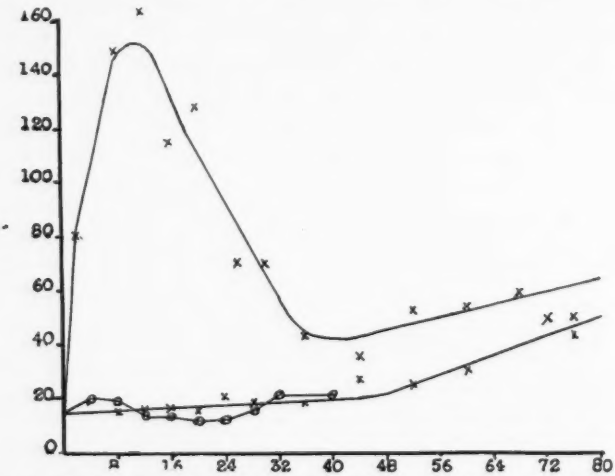

Figure 1. Weight of ovaries. Upper curve: rats given implants of two castrated male pituitary glands at 25 and 26 days of age. Lower curve: normal controls. Short curve: rats given implaint of one adult male pituitary at 26 days of age. Ordinates, milligrams weight; abscissa, days after operation.

on ovarian weight when one male pituitary was implanted, this does not mean that the ovaries of these animals return to normal function in a few days. There seems to be an after effect on the ovary or the uterus which appears to retard further oestrus cycles for some time. If the recipients (rats receiving one male pituitary implant at 25 days of age) were again treated with a liminal amount of tissue, as one adult male or four adult female pituitaries, there was, in most cases, a further increase in ovarian weight but cornified cells were usually not present in the vaginal smears.

When the initial dose of the hormone was large, as when two castrated male rat pituitaries were grafted into immature rats on the 25th and again on the 26th day of age, the ovarian weight sharply increased and at the end of about 12 days reached a weight of 162 milligrams in the experiment shown in Figure 1. After the 12th to 20th day, the ovaries began to diminish in size, first rapidly, then more slowly, but remained above

the controls until the latter reached sexual maturity (Fig. 1). If these animals were again subjected to potent pituitary implants, the ovaries were greatly enlarged, as shown in series C, Table 2, and not one of them showed cornified cells in the vaginal smears. It, therefore, seems that the greater potency of the initial implants, the greater the disturbance in the reproductive tract and the more difficult it becomes to produce oestrus.

It is interesting that the rats with the pituitary implants usually again came into oestrus at about the time the controls became sexually mature, and while the ovaries were still much heavier than those of the

TABLE 2

Body weight in grams; other weights in milligrams.
Age=age when killed.
Two castrated male pituitary glands implanted on days indicated.
Six to ten rats in each series. All figures averages.

Series	Age	Body	Ovaries	Uterus	Pituitary	Adrenals	Age When Implants Given
A	43	68	16	36	3.7	17.7	Normals
B	43	65	125	175	3.6	20.8	25th and 26th days.
C	43	65	228	360	4.6	20.2	25th and 26th, also 38th and 39th days.
D	43	66	120	110	4.0	18.5	38th and 39th days.

controls. At that time—60 to 80 days of age—the oestrus cycles were irregular in the experimental rats and cycles of 5 to 6 days in length were more uncommon than in normal rats.

The weight curve of the ovaries of rats treated with pregnant human urine and blood serum are shown in Fig. 2. The ovarian weights again remain higher than the controls for some weeks following treatment. The response in weight of the ovary in immature rats following the injection of

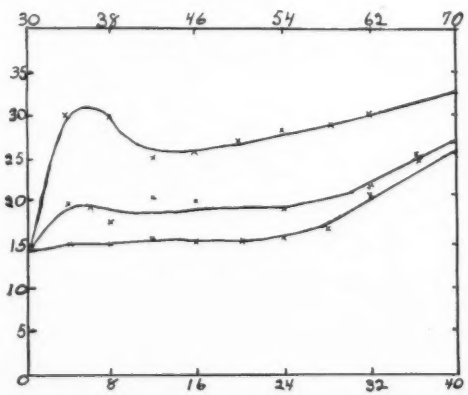

Figure 2. Curve of ovarian weights. Upper curve: rats injected with two cubic centimeters of pregnant human urine daily for four days beginning at 26 days of age. Middle curve: rats receiving five cubic centimeters of castrated male rat serum for four days beginning at 26 days of age. Lower curve: normals. Abscissa, above, age in days; abscissa, below, days after vagina opened. Ordinates, milligrams weight.

castrated rat serum is more variable than when pituitary grafts, extract, or urine are used. This may be due in part to the length of time the donors are castrated; at least, in the cases previously reported (Emery, 1932), when ovaries weighing 100 milligrams were produced by injecting serum, the donors had been castrated more than six months and at about 40 days of age. In recent experiments, using the same test, 30 cc. of serum injected into an immature rat in doses of 5 cc. daily, but with serum of donors castrated three to eight weeks, the ovaries have varied from 12 to 50 milligrams in weight.

WEIGHT OF UTERUS

The growth of the uterus following pituitary grafts was in relation to the amount of pituitary tissue implanted. When four castrated pituitary glands were implanted into each recipient, the uterus increased in these experiments to a mean weight of 263 milligrams on the 20th day following the last implant, while the uterus of the controls weighed 37 milligrams. Although the uterus varies greatly in size in both normal and grafted animals, these figures do show (Table 1) that the uterus increases in size for two or three weeks following the grafts and then decreases. At the age of about 85 days and older, the uterus of the grafted and control rats are similar in weight, and by this time the weights are less significant in both groups due to the oestrus cycles.

WEIGHT OF THE PITUITARY GLAND

The weights of the pituitary glands of the recipients in experiments where a total of four castrated male pituitaries were implanted at 25 and 26 days of age and no further implants made, have been compared to the controls of the same experiment. About 50 such pairs, taken from the data shown in table 1, have been studied and no significant difference found between the weight of the pituitary in experimental and control animals. In other implant experiments of a similar kind (table 2), the results confirm this. In animals given more frequent treatment, either with pituitary extract or in the regrafting experiments shown in series C, table 2, the pituitary glands tend to be slightly heavier than those of the controls. Analysis of the data showed the mean difference was four times the probable error of the difference. Due to the small number of rats in this series, these significant results may best be considered doubtful.

WEIGHT OF THE ADRENALS

In these experiments, the adrenal glands did not show an increase in weight when small doses of pituitary substance were given either as implants or as extract. Smith and Engle (1927) also failed to get enlargement of the adrenals with pituitary implants. However, when potent preparations were given either as extracts or pituitary implants from cas-

trated animals, there was some enlargement of the adrenals after several days or weeks following the treatment. In table 2, the adrenals of normal rats weighed 17.7, and those with pituitary implants (series B, C, D) 20.8, 20.2, and 18.5 respectively. From these data, the probable error of the difference was calculated and found to be three times the mean difference. Thus the difference in weight between the controls and grafted animals, although significant, certainly is not great. In other experiments, whole sheep pituitary extract (Parke-Davis)* was used in doses of 1 to 5 cc. This treatment did not cause as great a response in ovarian growth as did four castrated male pituitaries, and the effect on the weight of the adrenals was slight. Large doses, 25 units daily, of antuitrin (Parke-Davis) are, also, required to produce a noticeable increase in weight of the adrenals. Thus it seems that the dosage required for adrenal growth is many times the amount necessary for noticeable enlargement of the ovaries.

DISCUSSION

The experiments reported here deal for the most part with rather large doses of anterior pituitary glands given as implants or, in some cases, as extract to immature rats, usually for a period of two days' duration. Thus it is not surprising that there was no effect on the subsequent growth of these rats.

The primary object of these experiments was to see the lasting effect on the reproductive system of bringing immature rats to sexual maturity at 25 days of age. The ovarian growth was dependent upon the dosage of pituitary hormones given and reached its greatest size in about two weeks after four castrated male pituitaries were implanted, as shown in table 1. The time taken for this maximal growth following stimulation with anterior pituitary hormones depends on the potency or dosage of such hormones as is clearly shown in figs. 1 and 2. The maximal capacity of these immature rat ovaries for growth has probably never been reached, as shown by the grafting experiments reported in table 2. In other words, the ovaries have always responded by an increase in weight whenever castrated male pituitaries were grafted. In other regrafting experiments, ovaries weighing 500 milligrams, or about 1/100 of the body weight were obtained. Engle (1928) has also obtained ovaries weighing more than 300 milligrams by pituitary implants in rats.

It is again interesting to point out as others have done (Engle, 1929, and Evans, et al., 1932), that the response of the ovaries to larger doses of pregnant urine differs from that to pituitary implants. In these experiments, the maximal weight of the ovaries was obtained with a total of 8 cc. of urine given over a four-day period, as shown in fig. 2. Larger doses of urine did not further increase the weight of the ovaries. On the other hand, urine will not prevent the anterior pituitary sex hormone from causing enlargement of the ovaries (Emery, 1932).

*Kindly supplied by Dr. Kamm—Parke-Davis & Company.

In many experiments, first with semicastrated animals (Emery, et al., 1931), and later with blood and urine (Emery, 1932), it was observed that the uterus was often enlarged while the ovaries were no larger than the controls. In most of these cases, the immature recipient rat had manifested signs of oestrus, as represented by opening of the vaginal canal and cornified cells in the vaginal smears. This point raises the question of a direct action of the pituitary sex hormone on the uterus and vagina. Smith and Engle (1927) failed to induce growth of the uterus in castrated animals by pituitary grafts. Their observations are usually easily confirmed, yet there are cases which are not in agreement with them; a few rats showed questionable increase in uterine growth, but definite positive vaginal smears when given subminimal doses of theelin with either whole pituitary gland extract or pituitary grafts. A group of 30 castrated rats treated in this way at varying lengths of time following castration and continued under observation for several days or weeks showed a few individuals that gave definite positive reactions, as compared to the controls which received the same doses of theelin but no pituitary treatment. At autopsy remaining ovarian fragments were not found in any of these rats. These observations are difficult to understand and are, further, rendered difficult to explain, due to the theelin injected. The variability of the response to theelin is well known and our own observations support the idea expressed by Kennedy (1930), that "the unit concept is not, therefore, to be regarded as a fixed one." Hartman, et al. (1930), have described menstruation-like bleeding in monkeys following injections of pituitary extract. This observation was thought to indicate a hormone in the anterior pituitary gland different from those hormones that cause ovarian growth and corpus lutea development. Saiki (1932) failed to get bleeding in monkeys after ovariectomy and considers the menstruation-like bleeding to be brought about through follicular hormone from the ovaries. Smith (1932) attempted to determine if there is any difference in uterine growth produced by theelin injected into ovariectomized and hypophysectomized rats. In the small number of animals studied, there was no direct effect of the anterior hypophysis on vagina or uterus. In the light of these investigations, the direct action of pituitary sex hormones on the uterus or vagina seems doubtful.

The relationship of the adrenals and the pituitary gland, although long known to exist, is not at present well understood. The many references cited by Moehlig (1929) show clearly that hyperplasia of the pituitary gland results in hyperplasia of the adrenal cortex. Further proof of such a relationship has been recently shown by Atwell (1932) in hypophysectomized anura and rats. It was, therefore, not surprising to obtain evidence of increased weight in the adrenal glands following rather potent pituitary implants (table 2). Pituitary injections or implants given at more frequent intervals over long periods of time should show further increase in adrenal weight.

The question of how long these implants may function has frequently been considered. Smith and Engle (1927) were among the first to point out the need for repeated implants since the transplanted gland was rapidly resorbed. Likewise, in these experiments, it is very likely that the continued growth of the ovary for 12 days or more (table 1) was due to the hormones absorbed during the first and second day following the implant. In some cases, grafted tissue was thought to have been found at autopsy as long as two weeks after the implants were made; this tissue was not sectioned for histological study, and even if proven to be pituitary tissue, the question of hormone production from such fragments remains doubtful.

SUMMARY

1. Both the immediate and chronic effects of the anterior pituitary sex hormones on the reproductive tract of rats has been studied. Immature female recipients were used—100 received pituitary glands as implants, and 80 were injected with either urine of pregnant women or serum of castrated rats. The weights of the body, ovaries, uterus, pituitary gland and adrenals were obtained at various lengths of time following treatment and compared with weights obtained from a similar number of control normal rats.

2. The ovaries and uterus continued to increase in size for about two weeks and remained larger than the controls for about two months after four castrated male pituitary glands were implanted in the muscles of 25-day-old recipients.

3. The ovaries and uterus completed their growth in a few days, when less potent pituitary implants were made or when either blood serum or urine of pregnant women was injected.

4. The pituitary glands of rats receiving implants at 25 and 26 days of age were not heavier than those of the controls.

5. The adrenals were slightly increased in weight; body weight was not affected.

6. In young rats, when the background is a large reproductive tract induced by pituitary implants, further implants produced increased weight of these organs, but oestrus did not occur.

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THE ROLE PLAYED BY THE THYROID GLAND IN THE PRODUCTION OF GROSS BODY ACTIVITY

CURT P. RICHTER
Phipps Psychiatric Clinic, Johns Hopkins Hospital
Psychobiological Laboratory
BALTIMORE

The function of the thyroid gland has been widely investigated with regard to its effect on the basal metabolic rate of the animal body, but little attention has been given, experimentally, to its influence on the total activity of the organism as represented by work and play. Clinically it has appeared that hyperactivity of the thyroid is associated with an increase of spontaneous action, and hypoactivity, with sluggishness. However, our inability to estimate gross body activity in man in any quantitative sense has made it impossible to test the correctness of these clinical impressions. Several attempts have been made to reproduce the behavior picture of hyperthyroidism in animals whose activity can be measured, but hitherto all such attempts have brought contrary results. Hoskins (1927), working on rats, found that removal of the thyroid did not decrease their spontaneous activity, as measured by the distance run daily in a revolving drum, and Wang and Richter have obtained the same result (unpublished). Furthermore, Wang (1927), Hoskins (1927), and Lee and Van Buskirk (1928) found that feeding the desiccated gland to rats produced a decrease rather than the anticipated increase in activity. In view of this discrepancy between the clinical impressions and the experimental results, and because more adequate knowledge of the behavioristic phase of thyroid function is needed, particularly in psychiatry, it was decided to repeat the extirpation and feeding experiments, and to extend them so as to demonstrate any changes in food and water intake, body weight, and sex gland activity.

METHODS

The technique used has been described in previous papers (Richter, 1927). Each rat in its small living cage has free access to a revolving drum, the revolutions of which are registered on a cyclometer. That this gives a good measure of the activity of the rats may be shown by translating the revolutions of the drum into miles; many animals run as much as ten miles in twenty-four hours, and some run over twenty. The small cage in which the animal spends most of its time when not running contains a food-box with the McCollum diet and an inverted watering tube. Daily at noon, activity and food and water intake are measured and vaginal smears are made. Body weight is recorded weekly.

Four male and ten female rats were placed in activity cages when they were 30 to 40 days old. The activity of animals of this age is found

to be consistently lower than the normal adult average, but it mounts steadily after the first few days in the new cages, until a plateau appears, 20 to 30 days later. The thyroids were removed in the above animals either some time before or immediately after this plateau was reached; i.e., between 60 and 90 days of age, before full growth had been attained. Daily records were taken as described for as long as 10 months after extirpation of the glands.

The glands were dissected out as nearly as possible in one piece under a dissecting microscope. The two main parathyroids were removed at the same time, of course, but inasmuch as the rat has several other parathyroid glands besides those contained in the thyroid, the usual tetany symptoms did not appear and most of the animals survived the operation.

At autopsy this region was examined under the dissecting microscope for remnants of thyroid tissue. All suspicious bodies present were removed and preserved for histological study.

Desiccated preparations of the gland in tablet form were fed with the McCollum diet. The tablets were powdered in a mortar and thoroughly mixed with the food, 1-80 grains (0.064-5.12 gms.) to 1,000 grams of food. Calculations based on the food-intake records showed that the animal received daily from 1/13 to 6½ grains (0.005-0.400 gms.) of the desiccated substance per kilogram body weight.

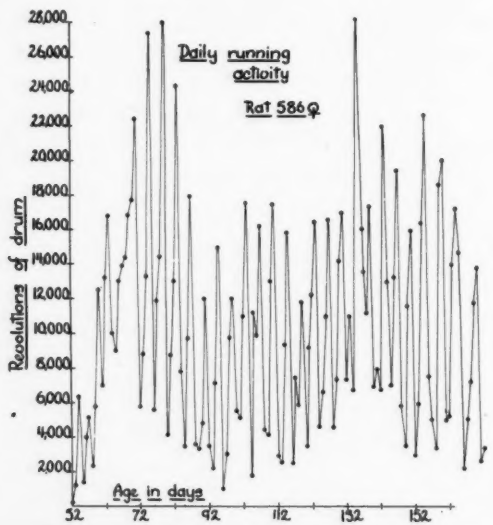

Figure 1. Graph showing running activity of normal female rat. The activity as measured by the number of revolutions of the drum is given on the ordinates, the duration of the experiment in days on the abscissae.

RESULTS

A. Effect of thyroidectomy and subsequent replacement therapy on spontaneous activity.

1. *Changes in amount of activity produced by thyroidectomy.* Widely differing results were obtained in these experiments. Some animals showed no effect at all, while in others there was a definite but moderate decrease in activity. Only one, a female, showed a sharp but permanent drop to almost total inactivity. Charts representing each of these three groups, with a record from a normal control animal, are presented for purposes of comparison in Figs. 1, 2, 3 and 4. The running activity in revolutions of the drum is given on the ordinates, the duration of the experiment in days on the abscissae. The record in Fig. 1, from a normal female, shows the

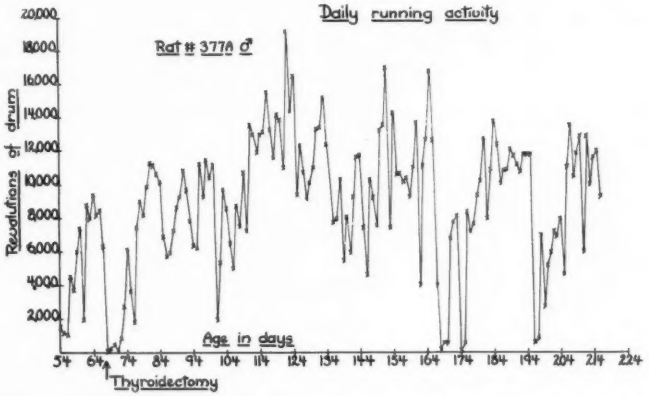

Figure 2. Graph showing the lack of any effect of thyroidectomy on the activity of one animal.

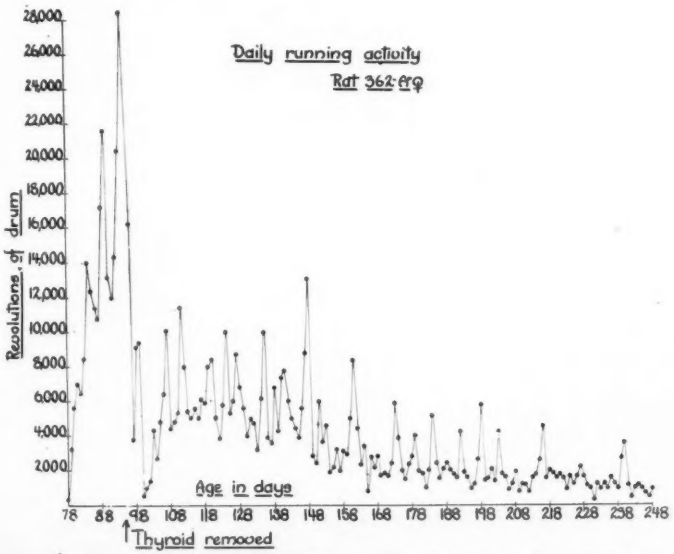

Figure 3. Graph showing marked drop in activity produced by thyroidectomy.

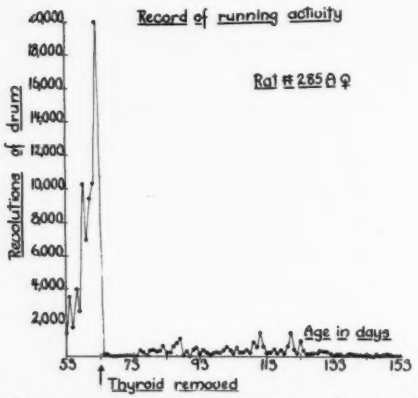

Figure 4. Graph showing very marked decrease produced in one animal by thyroidectomy.

usual increase occurring in the activity during the first two or three weeks in the running cages, and the subsequent plateau with the regular four-day ovulation cycles of activity superimposed. The activity of male rats is lower and more irregular but is not marked by the four-day cycle.

The graph in Fig. 2 shows the activity of a male animal which apparently was unaffected by thyroid extirpation. The rat was placed in the running cage at the age of 54 days, and from then to the time of the thyroidectomy at 67 days, it showed the usual steady increase in activity to a level of 7,000-8,000 revolutions per day. Immediately after the operation there was a drop to a low level for a few days, but the animal soon became active again and reached the preoperative average. Subsequently this increase continued and finally after 60 days a fairly high level was reached.

Fig. 3 illustrates the marked drop in activity which was produced by thyroidectomy in most of the rats. This very active animal, operated on when 95 days old, dropped in activity from a peak of 28,000 revolutions daily to a level near 6,000.

The curve, in Fig. 4, with a sharp decrease to almost complete inactivity, as noted above, was the only one of this kind obtained.

The results of these experiments are summarized in Table I, which gives the identification numbers of the animals; their sex; age at the time of operation; the average running activity for the 10 days preceding the operation and 50 days following; the pre-operative and post-operative average food and water intake; the percentage of change in these three factors; post-mortem isolation of suspicious bits of tissue in the tracheal region; and the result of histological examination of this tissue.

It can be seen that three of the four males showed no definite change in activity; one male and nine females showed decreases of varying magnitude but still remained fairly active; the activity of one female was reduced to a very low level of less than 600 revolutions per day.

In seven instances, isolated fragments of tissue, not necessarily thyroid, were found near the trachea at autopsy. Four of these fragments were too minute for sectioning. The other three, found in males, scarcely larger than a pinpoint, were preserved and found histologically to contain active thyroid tissue.

These experiments would seem to indicate that when a relatively small piece of thyroid tissue is left in the body, activity is unaffected; but that removal of all of the gland or all except an almost microscopic particle causes a definite but moderate drop in activity. The effect of thyroidectomy in rats, then, is similar to that in man. The failure of Lee and Van Buskirk, Wang and Richter to find a decrease in activity probably was due to the presence of pieces of unremoved thyroid tissue as large as those found in the three animals mentioned above.

2. *Fluctuations and cycles of activity produced by thyroidectomy.* The most striking effect of thyroid removal is not so much the actual reduction of activity as the production of a state of instability, characterized by extraordinary fluctuations, which in some instances appear in regular cycles. An example of these sharp changes which may occur in the activity level can be seen in Fig. 5. Such changes have never been found in normal animals under the experimental conditions described above.

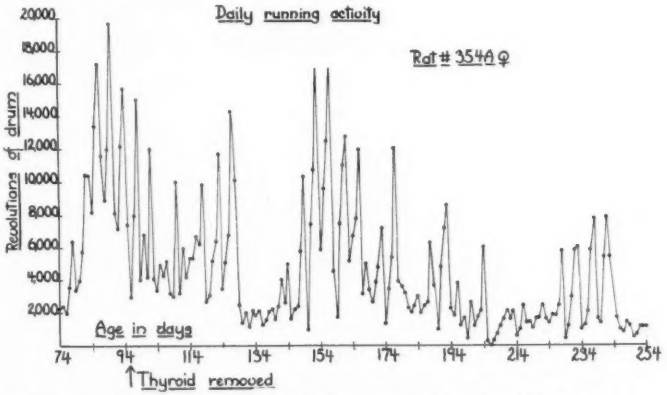

Figure 5. Graph showing the types of effect produced by thyroidectomy.

The best instance of regular cycles of activity, other than the five-day cycle, is presented in Fig. 6. Here, the waves lasting from 20-25 days, with the animal active for 5-12 days and then almost totally inactive for 10-15 days more, recur with great regularity. Thus, fairly definite peaks occur on the following days: 156, 196, 216, 260, 280, 306, 331 and 354. It will be noted that each long activity period usually contains several five-day periods. Cycles of the same length but of lesser regularity were observed in two other animals, the cycles becoming more regular and more clearly distinguishable as the animals grew older.

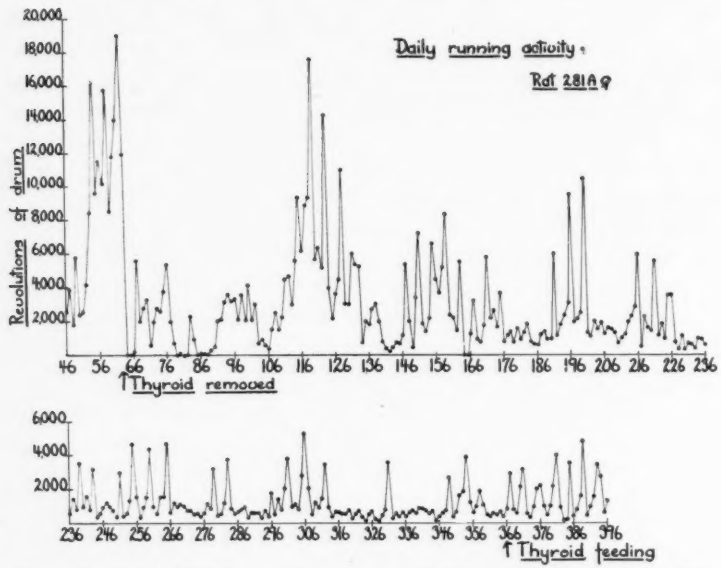

Figure 6. Graph showing the appearance of 20-35-day rhythm in activity after thyroidectomy. The record also shows the effect of feeding small quantities of desiccated thyroid gland.

3. *Effect of thyroid feeding on the activity of thyroidectomized animals.* In the early experiments thyroid was administered in doses of 20 grains (1.28 gm.) of the desiccated gland per 1,000 gm. of food, 1.0-1.5 grains (0.064 gm. per animal per day). This dose was smaller than that used by Wang and by Hoskins in some of their experiments, but it regularly gave the same result: the animals became almost totally inactive and remained so as long as the glandular extract was administered. A typical record of this reaction is shown in Fig. 7. Before the thyroid was admin-

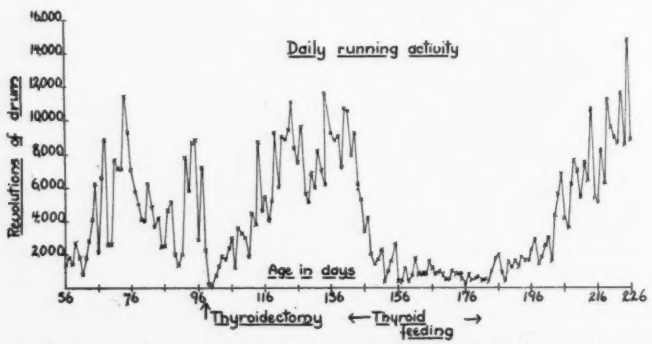

Figure 7. Graph showing the effect on activity of feeding large doses of desiccated thyroid gland to thyroidectomized animal. The activity dropped down to a very low level during the feeding and remained low for some time after the feeding was stopped. It finally returned, however, to its original high level.

istered the level of activity varied between 9,000 and 10,000 revolutions per day. During administration it dropped below 500 revolutions per day, but began to increase again almost immediately after the feeding was stopped, reaching its original level after 50 days. Similar results were obtained in ten normal, ten spayed, and fourteen thyroidectomized animals.

When, however, very much smaller doses were used (1-2 grains per 1,000 grams of food; i.e., 0.006-0.012 gm. per kilo body weight per day), entirely different results were obtained. The inactive thyroidectomized animals became active and tended to reach the normal level again. From the record in Fig. 8, it can be seen that before the thyroid preparation was

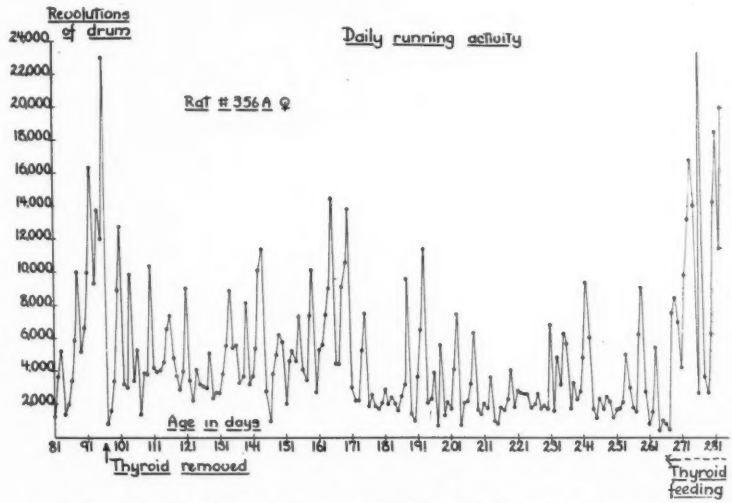

Figure 8. Graph showing a decrease produced in activity by thyroidectomy and a subsequent increase to normal produced by feeding small doses of desiccated thyroid gland.

fed, the level of activity varied between 3,000 and 4,000 revolutions per day. About 6 days after the feeding was started, the activity began to increase and soon reached the high preoperative level of 18,000-20,000 revolutions. It is interesting to note that the extract smoothed out the cyclical changes described above so that the activity remained on a more constant level.

These experiments definitely establish the fact that the reduction of activity after thyroidectomy is due to a lack of thyroid secretion, since replacement of this secretion restores the activity to its normal level again. They demonstrate further the importance of dosage, since large amounts of thyroid extract produce contrary results. It is possible that doses even smaller than 1 grain per 1,000 grams of food may be capable of replacing the amount of thyroid secretion necessary to re-establish the normal level of activity.

B. Effect of thyroidectomy and subsequent replacement therapy on body weight.

The results of these replacement experiments are in entire accord with the observations made by Smith, Greenwood, and Foster (1927), etc. There are a few facts, however, which may be added here. It was found, in agreement with their record, that thyroidectomy causes either a small decrease in growth or, in the growing animal, an arrest of growth. A typical record is shown in Fig. 9, with a curve from a control female. It

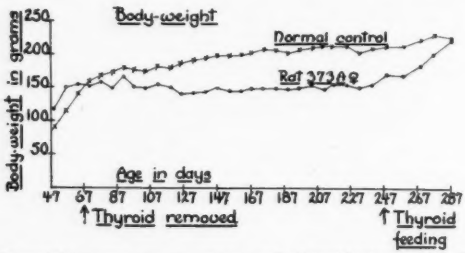

Figure 9. Body-weight curve in a male, and thyroidectomized animal, showing the effect of thyroid feeding.

can be seen that the thyroidectomized animal remained on an almost constant weight level for 90 days after the operation. Subsequent administration of the aforementioned small doses of thyroid extract, however, produced an immediate and rapid increase to normal weight.

It is interesting to note that the three animals which failed to show any decrease in activity, and in which small thyroid remnants were found, all showed the flattening of the growth curve just as the others did. Apparently growth can be more easily affected than activity and is not in itself a criterion of complete removal of the gland.

Large doses of thyroid gland which cause a decrease in activity produce a small decrease in body weight. In other words, with an oversupply of the extract, the animals lose weight just as does the patient with hyperthyroidism.

C. Effect of thyroidectomy and subsequent replacement therapy on food-intake.

Removal of the thyroid consistently produces a decrease in food-intake. The animals in which the activity was most affected showed the largest reduction in food-intake. The results of these experiments are summarized in Table I, which gives the average daily food-intake for 10 days before the thyroidectomy, and for 50 days thereafter. It can be seen that the food-intake of three of the males remained on practically a constant level, while in the fourth it dropped from 15 to 10 grams per day. All of the ten females showed decreases, ranging from 23 to 64 per cent. The food-intake of one animal dropped from 14 to 5 grams per day, and most of the others showed a loss almost as great.

TABLE I

Rat	Sex	Age in Days at Time of Operation	Average Daily Running Activity (In Revolutions)			Average Daily Food Intake (In Grams)			Average Daily Water Intake (In c.c.)			Suspected Tissue Found at Autopsy	Histological Findings on Autopsy Material
			10 Days Pre-operatively	50 Days Post-operatively	Per Cent of Change	10 Days Pre-operatively	50 Days Post-operatively	Per Cent of Change	10 Days Pre-operatively	50 Days Post-operatively	Per Cent of Change		
323 A	M	98	5,348	5,798	8.4+	11	12	9.0+	44	35	20.5—	Minute pieces	Too small for study
325 A	M	98	9,248	5,108	44.7—	14	14	0.0±	52	49	5.7—	Small piece	Active thyroid tissue
368 A	M	109	6,276	6,728	7.2+	16	14	12.5—	31	30	3.2—	Two small pieces	Active thyroid tissue
377 A	M	67	6,670	7,945	19.0+	15	10	33.3—	33	24	27.3—	Minute pieces	Active thyroid tissue
154 A	F	130	14,441	3,168	78.7—	16	7	56.2—	29	17	41.4—	Minute piece	Too small for study
281 A	F	63	12,538	1,990	84.1—	14	5	64.3—	28	23	17.9—	Minute piece	Too small for study
338 A	F	120	3,024	1,711	43.4—	13	10	23.1—	26	29	11.5+	None	.....
354 A	F	95	12,705	4,907	61.3—	16	9	43.7—	39	35	10.3—	None	.....
356 A	F	96	9,248	4,788	48.2—	10	6	40.0—	36	26	27.8—	Minute piece	Too small for study
362 A	F	95	15,221	5,620	63.1—	13	8	38.5—	25	27	8.0+	None	.....
371 A	F	96	5,153	2,502	51.4—	12	8	33.3—	31	34	9.7+	None	.....
373 A	F	67	8,056	2,658	67.0—	12	8	33.3—	39	32	17.9—	None	.....
378 A	F	80	15,605	5,718	63.3—	14	7	50.0—	26	24	7.7—	None	.....
285 A	F	63	7,049	599	91.5—	10	4	60.0—	21	8	61.9—	None	.....

This change in the food-intake curve can be clearly seen in the graph in Fig. 10. The record shown at the top, from a normal female and presented for purposes of comparison, shows the normal gradual increase in food consumption until a plateau is reached at 90 days of age. Records for males are essentially the same, except that the food-intake is consistently somewhat higher. The second graph is from one of the males that showed no appreciable change in activity, but a marked drop in food-intake. The third and fourth graphs demonstrate an even greater effect.

Apart from the reduction, food-intake curves show great irregularity after thyroidectomy. This can be seen most clearly in the third and fourth graphs in Fig. 10. The food-intake of the third animal became absolutely

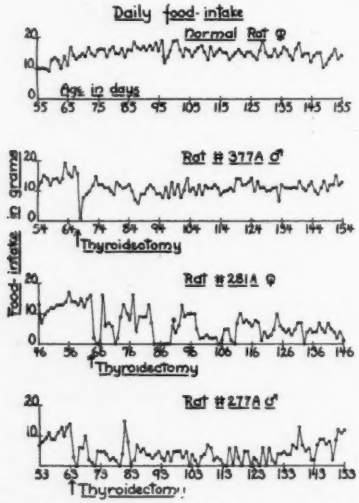

Figure 10. Graph showing effect of thyroidectomy on food-intake. A record from a normal animal is presented at the top.

irregular; thus, it went for intervals as long as 6 days without taking any food at all, only to eat fairly well again for a few days. The fluctuations are almost as great in the fourth graph.

Thyroid feeding consistently produced an increase in the food-intake of the thyroidectomized animals. The amount of the increase depended, of course, partly on how seriously the animals had been affected by the thyroidectomy, and partly on the size of the thyroid doses. The intake was usually brought to its normal level and the fluctuations eliminated by doses of 1 grain per 1,000 gm. of food. An increase of food-intake beyond the normal level was taken as an indication that the dose was too large.

D. The effect of thyroidectomy and thyroid feeding on water-intake. Water-intake was much less definitely and consistently affected than food-intake. Some of the animals drank more water, some less, after thyroid-

ectomy. There was a more general tendency toward a decrease, as may be seen in Table I, but the irregularities which characterized the food-intake were not so marked.

The effect played by the replacement therapy of thyroid depended on the dosage. Large doses had the same effect that they have on normal animals; i.e., they produced a very great increase in water-intake (see Fig. 11). Smaller doses which were effective in restoring the normal activ-

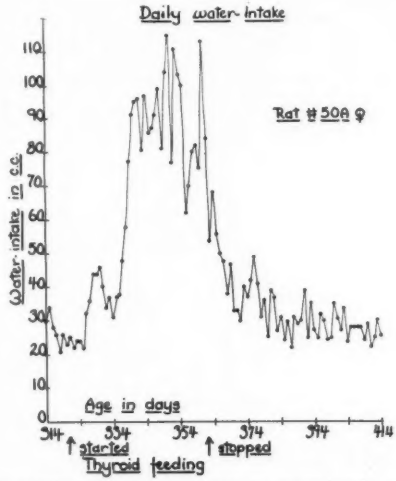

Figure 11. Graph showing the large increase in water-intake produced by administration of large doses of desiccated thyroid gland (.040 gm. per kilo.). It is to be noted that the water-intake began to increase a few days after the feeding was started and remained high for several weeks after it was discontinued.

ity had only this effect, that in several animals there was a temporary decrease, lasting about 10 days after feeding of the extract was begun.

The fact that removal of the thyroid does not produce a decrease in water-intake comparable to the decrease in food-intake, as much or more water being taken as before, may throw some light on the production of the myxoedematous condition.

E. The effect of thyroidectomy and thyroid feeding on the reproductive system of female rats.

The marked disturbances produced by thyroidectomy in the very regular four to five-day activity cycles, are summarized in Table II. The intervals between peaks of activity will be seen to vary from 3-25 days. There seems to be a definite relationship between the regularity with which these peaks recur and the average level of activity at the time. That is to say, when the animals are active the four to five-day cycles are quite regular; when they are inactive the cycles are either very irregular or absent altogether. This can be seen very clearly in the record shown in Fig. 6, with long 20-35-day cycles. During the inactive phase, lasting about

TABLE II

Rat	Normal		After Thyroidectomy		After Thyroid Feeding		Autopsy Findings	
	Activity Cycle in Days	Smear Cycle in Days	Activity Cycle in Days	Smear Cycle in Days	Activity Cycle in Days	Smear Findings	Ovaries	Uterus and Horns
154 A	5, 3, 4, 3, 5	.....	48, 3, 8, 12, 4, 4, 4, 5, 3, 5, 3, 4, 4, 4, 4, 4, 3, 5, 6, 5	.....	4, 8, 4, 3, 3, 3, 8, 5	Prolonged cornified stage	Oestrous; no corpora lutea; much interstitial tissue; atretic follicles	Oestrous; moderately large; no secretion, tall epithelium
281 A	4, 4	.....	9, 7, 15, 10, 4, 7, 4, 5, 5, 7, 9, 4, 4, 4, 4, 4, 4, 16, 5, 4, 16, 5, 4, 13, 4, 7, 4, 5, 5, 14, 4, 18, 6, 6, 20, 18, 5, 4, 9	20, 18, 5, 4, 14	4, 5, 5, 4, 4, 4, 4	Normal	Five corpora lutea; congested	Small; no fluid
338 A	4, 4, 4, 4, 5, 4	.....	4, 5, 5, 5, 4, 3	.....	.....	.....	Large	.....
354 A	4, 4, 4, 4, 4, 4	.....	8, 8, 5, 4, 17, 5, 4, 4, 5, 4, 7, 4, 12, 5, 3, 8, 25, 5, 5, 6, 19	12, 4, 4, 8, 6	6, 8, 4, 4, 4, 4	Prolonged cornified stage	Corpora lutea numerous; no room for anything else	Small
356 A	5, 4, 4	.....	3, 6, 6, 5, 7, 6, 5, 5, 5, 6, 4, 6, 5, 5, 6, 7, 5, 5, 5, 5, 5, 6, 12, 4, 7, 12, 5, 4	10, 11, 12, 4, 4, 4	5, 3, 4, 13	Slightly prolonged cornified stage	Dioestrous; corpus luteum; less interstitial tissue; fragmented egg	Lower epithelium
362 A	5, 5	.....	8, 4, 9, 4, 4, 8, 6, 7, 10, 12, 24	5, 3, 9, 12, 3, 9, 24	5, 4, 4, 4, 4, 4	Prolonged cornified stage	Congested; vascular corpora lutea	Very large; thick wall
371 A	4, 4, 4, 4	.....	4, 6, 5, 5, 6, 4, 4, 4, 3, 7, 4, 4, 4, 4, 8, 3, 5, 5, 4, 6, 4, 6, 4, 5, 6, 4, 6, 4, 7, 6, 5	4, 5, 6, 8	4, 5, 5, 4, 3	Prolonged cornified stage	Follicles atretic; no corpora lutea; interstitial tissue	Very large
373 A	4, 4, 4, 5	.....	4, 3, 6, 2, 33, 7, 5, 6, 7, 5, 7, 5, 5, 5, 5, 5, 5, 5, 5, 6, 21, 13, 4, 1, 5	22, 11, 5, 9	4, 4, 4, 6, 5	Prolonged cornified stage	Large; corpora lutea	Very large; epithelium low columnar
378 A	4, 4, 9	.....	12, 5, 6, 4, 4, 4, 4, 10, 7, 5, 5, 5, 5, 5, 5, 4, 7, 5, 5, 13, 4, 6, 11	4, 4, 4, 4, 4, 4, 4, 11	11, 4, 4	Prolonged cornified stage	Large	Very large
285 A	4	.....	24, 5, 19, 9, 3	.....	.....	.....	.....	.....

15 days, the four-day cycles are absent, while during the active phase, lasting about the same time, they are clearly present.

The vaginal smears studied simultaneously with the activity records show the same irregularity. Usually during the inactive period the smears give consistently a dioestrous picture with only epithelial cells and leucocytes, while during the active phase they show cornified cells at the peak of the four-day cycle. There is a tendency during the active phase, however, for the cornified cell stage to be prolonged beyond the normal interval.

Thyroid feeding in small doses has a very clear-cut effect on the four-day cycles, which appear again and are as regular as in the normal animal. Doses slightly too great bring out irregularities again, obliterating the cycles.

The smear findings, however, do not show the picture of normal adult animals. Cornified cells tend to occur almost all the time. In view of this prolongation of the cornified cell stage, it was not a surprise to find at autopsy that these animals all showed very markedly hyperthrophied uteri. In one animal the horns were over a quarter of an inch in diameter, very much larger than they ever are normally in the oestrous phase; the tubes were filled with fluid and the ovaries were larger than usual. Histological study of the ovaries in the various animals showed a wide range of difference. Most of the animals gave an oestrous-like picture, with absence of corpora lutea and much interstitial tissue, but some showed normal ratios of corpora lutea with fragmented eggs.

None of the animals was killed before the thyroid feeding was started, so no record is available of the condition of the ovaries and tract after thyroidectomy alone.

DISCUSSION

The results of these experiments introduce anew the question of the rôle played by the thyroid gland in the production of spontaneous, voluntary body activity. In previous papers it was assumed, on the basis of experiments by Hoskins, Lee and Van Buskirk, and Wang and Richter, that this gland does not have any important effect on activity, despite the fact that it does on general metabolism. It has been shown above that it has a very direct and important, though irregular influence over activity.

Insofar as the thyroid gland, when removed, produces a decrease in activity, it can be classed with the pituitary, the adrenals, and the sex glands. The decrease produced by the removal of these organs, however, is considerably greater, and the low level reached is maintained very constantly, uninterrupted by sudden bursts or cyclical changes in activity. It would appear, then, that the thyroid is not as essential for the production of activity as any of these glands, certainly not as essential as the pituitary, but seems to function in the body rather in a regulatory capacity. More light should be thrown on the question of its function by the fact that

only a minute remnant of the gland is sufficient to maintain the normal level of activity.

The appearance of the wide fluctuations and definite cyclical changes after thyroidectomy is, from the psychological point of view, the most interesting fact gleaned from these experiments. The basis for these fluctuations and cycles has not been determined. It may be that when the influence of the thyroid gland is removed, the rhythm of some other gland appears. Under normal conditions the thyroid as regulator would keep this other gland in check and thus prevent cyclical behavior. The pituitary, adrenals, and sex glands may justifiably be suspected, of course, but the only evidence at hand on this point is that changes take place in the reproductive tract of the female simultaneously with the cycles of activity. It will be recalled that the smear findings showed a dioestrous period during the inactive phase and an oestrous period during the active phase. It is hoped that some time in the future, when a large number of animals showing the various cycles is available, a histological study of all of their endocrine glands, at one time at the crest of the activity wave, and at another at the trough, will help to bring out some important relationships.

The observation of the extreme fluctuations and irregularities produced in daily activity and food-intake of rats by total or nearly total extirpation of the thyroid gland may give some clue to the origin of very similar conditions in psychiatric patients. Many patients show marked changes in activity from day to day, as well as the great variation in appetite seen in the rats (Fig. 10). The production of actual cyclical phases after thyroidectomy should give a clue to the origin of some of the very regular phasic disturbances seen in the psychiatric patients.

Ziegler (1930-1931) has given a good review of the literature on insanity in myxoedema, with an account of three patients who came under his own observation. He describes a great instability in these patients, with alternate manic and depressive manifestations. Other writers speak of periods of somnolence punctuated by manic attacks—a picture which greatly resembles that noted in the rats. The thyroid deficiency in Ziegler's patients was produced by roentgen-rays and sub-total removal, and for this reason was easily diagnosed. The observations made on the rats, the instability of activity, the great fluctuations in appetite, should be of some help in diagnosing patients with thyroid deficiency due to natural causes.

In the treatment of myxoedematous patients with thyroid extract, the data on the relative merits of large and small doses in the rats may prove significant. It is possible that past failures in replacement therapy have been due to the use of too large doses of the extract.

SUMMARY

1. A study was made of the effect of thyroidectomy on the gross body activity, food-intake, water-intake and the reproductive cycles of twelve rats, four males and eight females. The animals were autopsied and a

histological study was made of all suspicious pieces of tissue around the trachea.

2. The results depended on the amount of thyroid tissue that remained. Four animals in which a very small piece still remained, showed no change in activity, food-intake or water-intake, while eight in which all, or all except the most minute amount was removed, showed very definite effects.

3. The activity, as measured by revolving drums, was reduced, showing marked fluctuations, irregular in five animals, but strikingly regular (25-35-day cycles) in three animals. Food-intake was markedly reduced but water-intake only very slightly. The reproductive system was definitely affected as shown by the irregularity of the cycles (vaginal smears) and the findings at autopsy.

4. These effects were corrected, either entirely or in part, by replacement therapy of thyroid extract given in very small doses (2-3 mgm. per kilo. body weight per day—given with food). The animals became active, the irregular fluctuations disappeared, food-intake increased, and the five-day cycles became regular again.

5. Large doses of thyroid extract (up to 16 mgm. per kilo. body weight) had a different effect: the animals became less active, ate and drank very much, and lost weight. They showed a typical hyperthyroid condition.

6. It was pointed out that similar fluctuations in mental activity have been seen in myxoedema cases in man.

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A CASE OF SPONTANEOUS PIGMENT LOSS IN THE BROWN LEGHORN CAPON AND THE PLUMAGE REACTION TO THYROXINE*

MARY JUHN
Whitman Laboratory of Experimental Zoology,
The University of Chicago
CHICAGO

In the studies related to problems of sex pursued under the direction of Professor F. R. Lillie at the Whitman Laboratory of Experimental Zoology, the experiments for the most part have been carried out on the Brown Leghorn fowl and thus numerous examples of this breed have been under observation for varied periods of time.

At intervals, particularly among the capons, an individual has become noticeable because of the relatively conspicuous distribution of white feathers among the normally orange and black plumage. This white feathering seems to appear first in the region of the head and of the neck-hackles, but it was also evident in the wing feathers, especially in the primaries where either white patches appeared or else the entire vane became involved.

While these birds were severally remarked on and the general plumage appearance noted, no particular attention was devoted to the feathering until recently, when an entirely white individual was brought to my attention by the poultry caretaker, Mr. Stange.

This bird, capon 29-942, was received in the laboratory as a one-day chick and reared under the standard conditions adopted here. It was caponized at about six weeks of age and when fully mature employed in a series of experiments on the effects of the chemically prepared female hormone on the plumage (Juhn, Faulkner and Gustavson, '31). The capon was in excellent shape during all the time of experiments and never showed any trace of abnormal behavior. It was last treated in December, 1929, and since then kept with the rest of the flock in large pens. The feathers were stated to have become slowly and progressively white during the year 1931, the median coverts over the secondaries being the last to change from the normal rusty-red coloring of this region.

At present the capon is entirely white; the feathers in all parts of the body are beautifully developed and accord entirely in their outline and structure—to minute details such as the normal mirror-imaging in the right and left feather pattern in certain tracts—with the structure of the normal plumage of the Brown Leghorn. The process of change involves

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the pigmentation only and does not concern the structural feather characteristics.

Since the capon was not under continuous observation during the time of color loss in the plumage, the actual course of the process was not followed. It is not probable, though, that depigmentation can occur in any save growing feather sections and in this connection it may be pointed out that in both head and neck of the capon, the regions where the first appearance of white color was most frequently noted, young, developing feathers are always abundantly present.

A case of complete change to white in a Black Leghorn hen has been described by Crew (1922). The plumage of this bird became white in the course of a year; the feathers of head and neck being affected first. The feather modifications in this bird were accompanied by a tendency towards the assumption of male characteristics, the head furnishings became enlarged and congested, the bird crowed and a few of the neck-hackle and saddle-hackle feathers were definitely cock-like in appearance and structure. The bird seemed ill for some months and finally succumbed to an internal hemorrhage; the postmortem examination showed the presence in the site of the ovary of a large tumor. The adrenals could not be found; it was thought they had become incorporated in the tumor, and Crew considers it possible that the progressive destruction of the adrenals was responsible for the gradual change from black to white and that the complete destruction resulted in the death of the bird.

A similar case of progression to complete depigmentation, involving first the head and neck and last the large tail feathers, has been described for a capon having brown plumage originally, and for a black hen; the capon remained entirely white but the female later became a light buff (Hesse, 1927). Doubtless a special examination of the literature would increase the number of these records.

The cause, in general, of this assumption of white plumage is for the present obscure. Crew's hypothesis, while possibly entirely valid for his case, does not apply to the capon No. 29-942, described here, the bird being remarkable, if anything, for his good condition. The possibility of the injections of female hormone in some manner being an effective agent in its plumage change to white is rather contradicted by the similar findings in other individuals not so treated.

That hyper-activity of the thyroid might play some rôle in this process of depigmentation at first seems plausible because of the results of Zawadowsky (1925). Zawadowsky fed fowls heavy doses of thyroid which caused a precipitate moult followed by the regeneration of white feathers having a somewhat looser texture than the ones replaced. However, the thyroid can probably be neglected here as the following considerations will show: All observers, working either with the desiccated gland orally administered (Torrey and Horning, 1925, pp. 371-4), or with subcutaneous injections of thyroxine (Lillie and Juhn, 1932, p. 170), have reported that

even very low doses, very considerably less than required to call forth the moulting and bleaching described by Zawadowsky, cause specific structural changes in certain feathers, and that the same response in increased measure is also produced with increase in dosage. The reaction occurs in the feathers having normally a margin of barbs free of barbules such as the hackle, back and saddle feathers of the male and the hackle feathers of

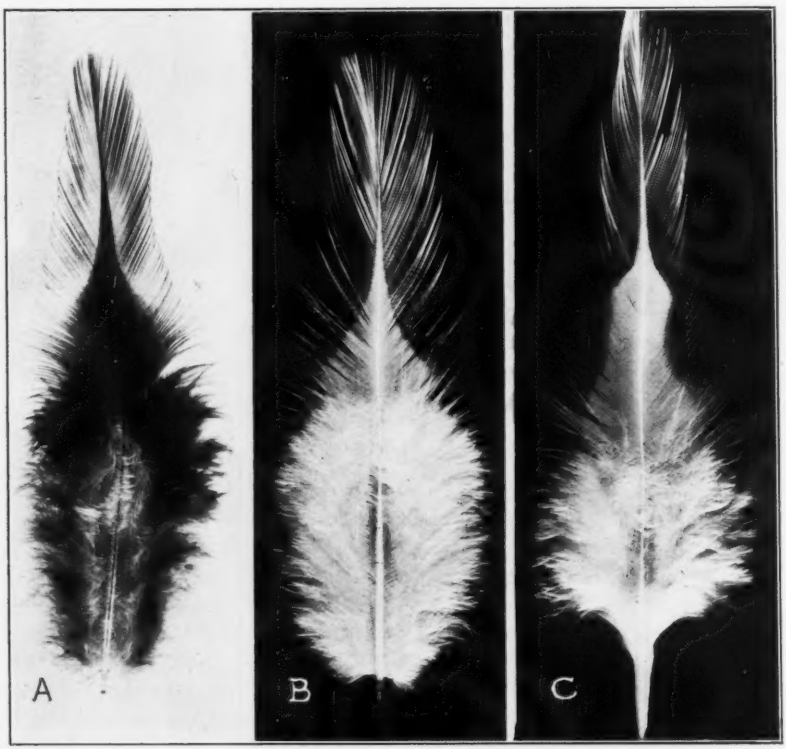

Plate I—Explanation of Figures

Figure A. Capon 29-942. Photograph of feather from back showing original normal pigmentation. 11-29-29.

Figure B. Capon 29-942. Photograph of feather from back showing complete color-change to white. 11-4-31.

Figure C. Capon 29-942. Photograph of feather from back illustrating the formation of barbules in barbs normally free in response to the injection of thyroxine. Protocol: 11-4-31, feathers plucked. 11-20-31, injected subcutaneously with 2 mgm. Squibb's crystalline thyroxine.

the female. In these feathers the administration of as little as 1.0 milligram thyroxine will cause the appearance of barbules in barbs originally deficient in these, producing a characteristic pattern which is readily recognized.

The process of color-change from the normal for the breed to white is a very gradual one, extending over many months and indicating a con-

tinuous action of some agent to which all the feathers developing during this period were exposed. But none of the modified, white feathers, showed the extra-regional formation of barbules which appears to constitute a response to thyroid gland or thyroxine administration and it therefore seems justifiable to rule out oversecretion of this gland as participant.

In pigmented breeds, such as the Brown Leghorn, the formation of barbules by thyroid feeding is associated with a deposition of melanin in these barbules (Horning and Torrey, 1927, p. 223) and the same is true for thyroxine, though it is possible by using very dilute concentrations to obtain barbule formation only (Lillie and Juhn, 1932). This dark pigment, while foreign to the position in which it is determined, is present in a latent state. It is similar to the melanin pigment normally occurring in the base of the feathers of the neck, saddle, etc., or in other regions of the bird's plumage, and its appearance in apical sections of saddle feathers for instance, is to be considered more reasonably in the nature of a displacement rather than a new formation.

This point of view is supported by the impossibility, so far at least, of obtaining a melanin reaction in normal white fowls. In their description of the darkening of feathers in Brown Leghorns, Barred Rocks, Campines and Rhode Island Reds, Horning and Torrey say (1927, p. 223): "White Leghorns show similar changes in feather form and structure, though not in color."

I have given two White Leghorn cocks a single injection each of 2 mgm. thyroxine (0.5 mgm. will cause melanin deposit in the Brown Leghorn) and in the hackle and saddle feathers have obtained the characteristic formation of barbules extending from the rhachis towards the margin of the vane, but no modification in color from the normal white. The breast feathers of these birds showed, as was to be expected, no change. Since these possess barbules to the tips of the barbs they consequently have no mechanism of response.

The capon, 29-942, while identical in plumage appearance, differed from these two males in being pigmented originally, and the reaction here to thyroxine was tested by the usual method of plucking feathers in hackle and saddle and the injection of a single dose of 2 mgm. thyroxine when regeneration was under way. The response proved entirely similar to the reaction in the pure-bred White Leghorns, distinct barbule formation took place, but the white color remained unaltered (Plate I, Figures B and C).

From the description of the female in the literature (Hesse, 1927), the plumage change to white is not an irreversible process and it is possible that in earlier periods, when the loss of pigment was only commencing in certain regions, a melanin reaction in the capon might have followed the administration of thyroxine. This can be tested if similar material appears in the laboratory.

SUMMARY

An instance of complete depigmentation occurring in the feathering of a Brown Leghorn capon is described. The process of color-loss was a gradual one, extending over a period of months and was not accompanied by structural changes in the plumage or any abnormality in the bird.

The probable non-participation of the thyroid in this bleaching of the feathering is discussed and experimental plumage modifications obtained with thyroid and thyroxine administration are listed for comparison.

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THE RELATIONSHIP OF IODINE TO THE BASAL METABOLIC RATE AND TO THE CHANGES IN THE THYROID GLAND IN PREGNANT RABBITS—AN EXPERIMENTAL STUDY

JAMES D. STEWART, M.D.
AND
FRANK R. MENNE, M.D.
From the Department of Pathology, University of Oregon Medical School
PORTLAND, OREGON

The changes in the thyroid gland during pregnancy have held the interest of clinicians and pathologists for many years. The problem is especially recognized in the goiter districts, where without early prophylaxis, thyroid disturbances are inevitable. By clinical observation and laboratory tests, variations in thyroid function during pregnancy have been estimated. Iodine is given throughout pregnancy to minimize such functional disturbances. That such administration is justified is common knowledge and is supported by the mass of current literature dealing with this subject.

It is an established fact that pregnancy is associated with a considerably exaggerated metabolic rate. This has been recognized by clinical observation for many years but was not established definitely until recently. The earliest determinations are quoted by Root and Root (1) as a relative and absolute increase in the oxygen consumption per kilogram of body weight, early in pregnancy.

In recent years more accurate determination with standard apparatus affords definite percentage increase of the basal metabolic rate in pregnancy. In 1921, Baer (2) reported 44 cases and in 1923, Cornell (3) detailed 84 instances with uniform results. They recorded a range of 29 to 35 per cent increase in the B.M.R., ante-partum with a sharp post-partum fall. Root and Root (1) cite one case with similar recordings. The study of patients with abnormal glands by Plass and Yoakman (4) in 1929, indicates that the ante-partum increase of the basal metabolic rate was influenced directly proportional to the degree of disease present. Their figures for augmented rates were similar to the above. Kraul and Halter (5) and Litzenberg and Casey (6) further substantiate these findings in their reports of decreased metabolic rates in instances of decreased genital function, dysmenorrhea, and sterility.

There is abundant evidence of the existence of thyroid hypertrophy during normal pregnancy, in the writings of Cornell (3), Plass and Yoakman (4), Braun (7), Rayeraft (8), Davis (9), and Straus and Daley (10). There are investigators who do not agree, however, notably Kraus (11) of Berlin. He states that the results of ephredrine injection tests

for thyroid function show a depressed rather than an intensified thyroid activity during pregnancy. In support of this view he reports three cases of patients dying intra-partum in which the histological picture of the thyroid gland was that of hypothyroidism. No such observations are found in the American literature.

Experimental studies of thyroid activity and associated abnormalities are probably more numerous than strictly clinical investigations. In the great mass of animal experimentation reported in the current literature concerned with the thyroid and its function, there are very few dealing with the problem presented here. There are, however, a number of papers presenting the results of iodine administration during pregnancy. In 1917, Smith (12) fed iodine and thyroid to pregnant sows. He found that five grains of potassium iodide daily throughout pregnancy, increased the number and vigor of the young. A similar amount of sheep's thyroid had little effect. The animals not receiving iodine or thyroid had only a few young, many of which died. Evard (13) in 1928, gave large doses of potassium iodide to pregnant ewes and found that the resistance of the young was decreased, fetal mortality was increased, but the incidence of goiter diminished. Carefully controlled experiments indicated that the larger the dose the greater the deleterious effect.

There are very few discussions or reports of the influence of iodine on the heat production in animals. Marine, et al. (14) in 1927, studied the effect of large doses of iodine on the heat production in rabbits. These investigators found a decrease in five instances, no change in 11, and an accentuation in two animals. No distinctive microscopic changes were noted. Cordonnier (15) caused an elevation of the metabolic rate in guinea pigs by feeding them desiccated thyroid. In these animals potassium iodide did not effect the return to normal.

The clinical results of iodine administration in cases with high metabolic rates, are well known and established. In 1924, Plummer and Boothby (16) reported 600 cases of Graves' disease in which the oral administration of Lugol's solution caused the basal metabolic rates to drop from dangerous heights to a point compatible with an excellent surgical risk. Marine (15) later pointed out that iodine in any form will involute physiological hyperplasia of the thyroid and prevent its occurrence in all of the different animals studied. He attributed this involution to increased colloid storage, distention of the acini, and an acute blocking of the peri-acinar capillaries and lymphatics, thus damming back the secretions.

There can be no doubt of the clinical value of iodine administration during pregnancy, as is witnessed by the many reports in the current literature. There is, however, a lack of controlled animal experiments and observations regarding the use of iodine. For this reason it seems justifiable to report the results obtained by the administration of iodine to rabbits during pregnancy and puerperium.

EXPERIMENTAL STUDY

The object of the study was to determine whether or not iodine has any significant stabilizing effect on the thyroid glands of rabbits during pregnancy. It was deemed advisable to establish certain conditions to be fulfilled during the course of the study. (1) The quantity of iodine to be administered was calculated according to the physiological optimum, and multiples of it were given daily by mouth. (2) Frequent basal metabolic rates were taken to note the effect on oxygen consumption and heat production. (3) Biopsies were made at term and at the end of lactation to determine the influence on the structure of the thyroid gland.

Thirteen rabbits were used. To these animals multiples of the physiologic iodine requirements were administered daily. Pregnancy was induced in nine of the rabbits, and these were followed through pregnancy and puerperium with frequent basal metabolic readings. The animals were kept in clean cages, in a moderately warm room, with good light, adequate food, and plenty of water. The feeding time was 2:00 P.M. and the basal metabolic determinations were taken the following morning so that 18 to 20 hours elapsed after feeding. The rabbits were carefully transported to the apparatus to avoid increased activity. A McKesson metabolor with circulating motor and water sealed breathing chamber was used to determine the oxygen consumption (Figure 1.) This apparatus

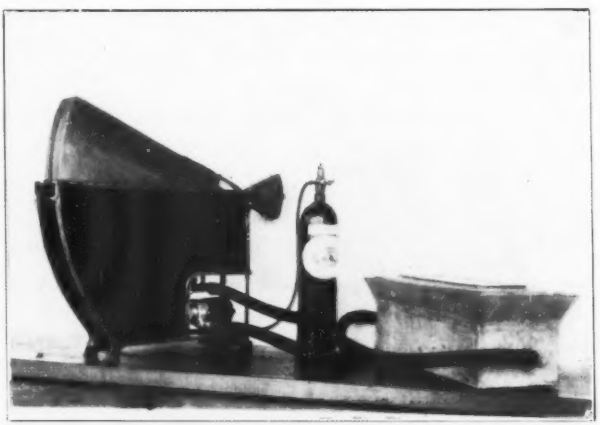

Figure 1. Photograph of the McKesson Metabolor and the water sealed breathing chamber used in the experiments.

was tested before each series of estimations and readings were taken only when it was found to be air-tight. This test period lasted 15 minutes. Wilson's soda lime for metabolors was used in the lime chamber. Fresh air and one liter of oxygen were used for each estimation. The rabbits remained in the breathing chamber for 15 minutes before the readings were taken. The weight in kilograms, the temperature, the barometric

pressure, and cubic centimeters of oxygen used were noted on a separate chart for each rabbit. Notes were also made regarding the condition of the animal and the probable approach to the basal condition. The animals soon became adjusted to the breathing chamber and remained in it for 30 minutes without a move.

The calculations were made with logarithmic tables that read to the sixth place. Meeh's formula for the surface area of animals was used. It is $S=KW^{\frac{2}{3}}$, when S is the surface area, K is a constant, and W the weight in kilograms. The constant for rabbits is 0.128. The surface areas of these animals averaged about 0.25 sq. m. Hayden's table temperature and barometric pressure corrections were used in the calculation of the basal metabolic rates. The basal metabolic rate may be defined as the calories produced per hour, per square meter of body surface area under standard conditions. The actual calculations were as follows: cubic centimeters of oxygen used per minute, times the correction factor in Hayden's table, divided by the fraction of a square meter of body surface area. The rates for each animal are given in the table marked Chart III.

The rabbits were given from one to five times the physiologic optimum of iodine requirements. This was administered in the form of Lugol's solution diluted 1/10000. Physiologic iodine is based on the quantity given by Sollmann (17), as about 0.045 mgm. for an adult in 24 hours. In each minim of Lugol's solution there are 6.5 mgm. of iodine. In one minim of a 1/10000 solution there would be 0.00065 mgm. of iodine or the amount required per kilogram of body weight in 24 hours. Thus for each kilogram of weight the rabbit was given 1, 2, 3, 4, or 5 minims of 1/10000 Lugol's solution. Rabbits 8, 9, and 10 were control subjects and received no iodine.

On the day following delivery one lobe of the thyroid was removed surgically. The other was extirpated at the end of lactation when the animal was sacrificed. There were no ill effects noted from the operation at term. The glands were fixed in Zenker's fluid, embedded in paraffin, and stained with hematoxylin and eosin. The histological description of each gland is given in order of presentation. See Chart II and composite table of the results, presented below.

Rabbit No. I received physiologic iodine daily for 15 weeks. She bore four healthy young in the tenth week. The microscopic sections of the lobe of the thyroid removed at term disclose small irregular acini, lined with low cuboidal epithelium and filled with pink vacuolated colloid. At the end of lactation the thyroid was made up of small, closely compact acini lined with cuboidal epithelium and filled with bright pink colloid.

Rabbit No. II received twice its physiologic iodine requirement for a period of two months. She became pregnant early and at the end of the first month delivered seven healthy young. Microscopic sections of the gland removed at term disclosed irregular small acini lined with low cuboidal epithelium and filled with pink, pale non-vacuolated colloid. The

CHART II

COMPOSITE TABLE OF THE EXPERIMENTAL DATA.

Rabbit No.	Quantity of Iodine Per Kilo	Normal B. M. R.	Pregnancy or Condition	Per Cent Increase B.M.R. in Pregnancy	Condition of Thyroid	No. of Young	Per Cent Decrease in Lactation	Condition of Thyroid
R-I	.00065 mg.	24.963	Pregnant	32.9%	Active	4	27.58%	Active
R-II	.0013 mg.	27.188	Pregnant	27.3%	Inactive	7	52.31%	Slt. act.
R-III	.0013 mg.	20.15	Pregnant	23.5%	Inactive	8?	0.	
R-IV	.00195 mg.	21.251	Pregnant	21.17%	Inactive	5	23.22%	Inactive
R-V	.00195 mg.	21.121	Pregnant	3.6%	Slt. act.	8	6.4%	Inactive
R-VI	.0024 mg.	23.98	Pregnant	27.2%	Inactive	3	48.7%	Inactive
R-VII	.00305 mg.	27.287	Pregnant	14.4%	Inactive	9	44.04%	Inactive
R-VIII	None	20.5	Pregnant	39.2%	Mod. act.	6	0.	
R-IX	None	25.81	Pregnant	45.1%	Active	2	79.09%	Active
R-X	None	21.767	Not preg.	0.	Inactive	0	0.	
R-XI	.00065 mg.	24.02	Not preg.	0.	Inactive	0	0.	
R-XII	.0024 mg.	20.02	Infection	0.	Very act.	0	0.	
R-XIII	.00305 mg.	25.59	Infection	0.	Active	0	0.	

blood vessels were engorged and the lymph spaces were dilated. The microscopic picture at the end of lactation was essentially the same.

Rabbit No. III received twice its physiologic iodine requirement or 2.0 minims of 1/10000 Lugol's solution daily for 266 days. She did not become pregnant until the last month of the experiment and the first day post-partum contracted an infection and died. The thyroid gland removed at autopsy was composed of relatively uniform, small acini filled with pale blue colloid. This colloid was peripherally vacuolated. The acinar cells were cuboidal and not infolded.

Rabbit No. IV was given 3 times the physiologic iodine requirement for a period of 233 days. Pregnancy occurred in the second month and she delivered the following month. One gland was removed on the first day post-partum and the mother devoured her young on the second day so that the post-lactation gland could not be studied. She did not become pregnant again so was killed at the end of the experiment and the remaining lobe removed. The thyroid removed at term was inactive microscopically. It was composed of small irregular acini with non-vacuolated colloid. The lobe removed at the end of the experiment showed no microscopic changes of note.

Rabbit No. V received 3.0 minims of 1/10000 Lugol's solution daily for 17 weeks. She became pregnant in the second month and bore eight healthy young. The microscopic sections of the thyroid removed at term revealed irregular sized acini lined with low cuboidal epithelium and filled with slightly vacuolated pink colloid. At the end of lactation the remaining lobe of the thyroid was found to be slightly enlarged. Microscopically

it was made up of uniformly small acini lined with low cuboidal epithelium and filled with non-vacuolated colloid.

Rabbit No. VI received four times the physiologic iodine requirement daily for 17 weeks. She became pregnant early, delivered three young and killed them soon after. After delivery the thyroid was removed. She did not become pregnant again so was killed at the end of the experiment. The thyroid removed at term was microscopically inactive. The acini were uniformly small, lined with low cuboidal epithelium, and filled with

CHART III

ALL B. M. R. RECORDINGS WITH THE AVERAGE RATES OF THE DIFFERENT RABBITS AND THE PER CENT OF INCREASE DURING PREGNANCY.

R-I	R-II	R-III	R-IV	R-V	R-VI	R-VII	R-VIII	R-IX	R-X	R-XI	R-XII	R-XIII	
26.34	36.49	37.70	23.11	33.66	25.54	29.34	24.32	26.88	20.35	21.15	20.83	25.29	
22.07	27.11	23.51	18.92	26.66	25.51	29.01	21.42	24.81	19.41	19.66	20.80	25.59	
23.44	29.06	23.60	19.01	34.50	23.72	30.52	18.76	24.90	21.54	24.77	20.02	25.34	
23.04	34.62	26.83	22.01	38.10	26.96	30.61	20.90	25.14	19.60	18.87	20.03	24.77	
22.58	23.71	28.40	21.76	29.53	29.28	25.31	18.96	31.10	18.98	23.91	20.15	21.98	
22.96	23.52	23.78	19.42	27.41	29.28	29.08	22.04	26.58	18.49	23.66	21.76	23.44	
21.00	22.63	27.55	20.61	30.53	23.59	24.29	20.71	27.05	22.02	21.65	21.63	24.71	
21.29	20.34	25.92	20.73	27.17	23.24	22.98	23.93	26.62	21.77	26.85	19.80	27.05	
23.87		28.48	19.50	30.23	30.20	25.06	27.83	37.66	19.57	24.22	20.55	27.51	
23.98		27.65	22.89	32.16	24.19	25.71	28.59	26.81	21.80	22.53	24.44	27.11	
33.38		27.48	25.75	32.24	25.98	31.27		25.11	23.60	20.99	30.52	24.54	
30.35		25.12	22.88	32.05	23.04	29.63		22.34	23.34	27.27	30.31	23.81	
29.35		25.95	21.73	30.32	22.93	28.92		19.15	21.70	24.99	33.99	24.92	
26.50		24.71	22.14		19.60	20.25		17.25	21.95	23.82	28.71	21.58	
		26.70	20.63		18.94				21.70	27.80		24.15	
		23.04	20.19		18.00				21.61	25.06		22.55	
		24.16	20.62		17.60				21.30	22.59		26.13	
		23.97	20.64						23.47	21.31		33.28	
		22.88	19.08						22.62	21.78		27.37	
		22.37	23.39						24.70	17.93		27.37	
		21.91	22.28						23.41	21.81		21.86	
		19.06	22.00						23.35	17.42			
		26.20	18.62						24.20	27.22			
			19.01						23.74	21.87			
			21.08										
24.96	27.18	20.15	21.25	31.12	23.98	27.28	20.50	25.81	21.76	24.02	20.02	25.59	Avg. Rate
32.90	27.30	23.50	21.17	3.60	27.20	14.40	39.20	45.10	.....	.....	.....	.....	% Increase

pale non-vacuolated colloid. At the end of the experiment the thyroid was made up of small collapsed acini containing no colloid. The acinar epithelium was disintegrating, the cytoplasm was granular and the nuclei very pale.

Rabbit No. VII received five times the physiologic iodine requirement daily for 14 weeks. She bore nine healthy young and passed through an uneventful pregnancy and puerperium. The thyroid removed at term was composed of irregular sized acini, containing abundant colloid. This colloid was pale pink and non-vacuolated. The same picture existed at the end of lactation.

Rabbit No. VIII, one of the controls, was treated similarly to the others except that she received no iodine. She delivered five healthy young but she did not care for them and they all died. For this reason only the term thyroid could be obtained. This gland presented microscopic evidence of activity as the acini were small, lined with cuboidal and columnar epithelium, and filled with vacuolated colloid.

Rabbit No. IX, also a control, was kept under conditions similar to the experimental animals except that iodine was omitted. She was carried through pregnancy and lactation. The thyroid removed at term appeared hyperemic. It was composed of small acini lined with columnar and cuboidal epithelium, and filled with scant vacuolated colloid. There was evidence of well marked activity. The gland removed at the end of lactation was less cellular, the acini being larger and the colloid more abundant. The colloid was markedly vacuolated.

Rabbit No. X, a control animal, received no iodine and did not become pregnant. She was under observation for 233 days. The thyroid gland removed at autopsy was grossly and microscopically inactive. The acini were small and closely compact. They contained but little non-vacuolated colloid.

Rabbit No. XI received the physiologic iodine requirement for a period of 231 days. She did not become pregnant and was killed at the end of the experiment. The thyroid consisted of two small reddish-brown lobes. Microscopically these were made up of uniformly small acini lined with low cuboidal epithelium, and filled with scant pale pink non-vacuolated colloid.

Rabbit No. XII was given four times the physiologic iodine requirement for 113 days. This doe never became pregnant but she took the male several times. She died on the 113th day after a prolonged course of furunculosis and a terminal septicemia. The thyroid gland removed at autopsy was very small and reddish-brown. Microscopically the thyroid was active as it was made up of irregular small acini lined with cuboidal and columnar cells, and filled with vacuolated colloid.

Rabbit No. XIII received five times the physiologic iodine requirement for 226 days. She did not become pregnant in spite of repeated attempts. During the sixth month of the experiment she contracted snuffles and died on the 226th day. The thyroid removed at autopsy was macroscopically unchanged. Microscopically the acini were small and of uniform size. The acinar cells were cuboidal and not hyperchromatic. The colloid was peripherally vacuolated and took a dull blue stain.

COMMENT

A summary of the findings in this experimental study includes certain data of note. There were 13 animals used. All of the rabbits except Nos. VIII, IX, and X received iodine daily as recorded on the composite chart (Chart II). It will be noted that Rabbits I to IX, inclusive, became pregnant and all showed a definite increase in the B.M.R. at term. R-X never became pregnant and received no iodine. Its B.M.R. remained within normal limits and its gland was microscopically inactive. R-XI received the physiologic optimum of iodine, did not become pregnant, and presented an inactive gland when sacrificed at the end of the experiment. Rabbits XII and XIII became infected and succumbed before pregnancy

occurred. These animals exhibited a sharp rise in their B.M.R. with the infection and at death the thyroid glands were found to be very active. The normal basal metabolic rate listed for each rabbit is the average of several readings taken under uncomplicated conditions, as there are no definite figures available for oxygen consumption and heat production in rabbits. The increase in the B.M.R. with pregnancy ranges between 3.6 per cent and 32.9 per cent in the experimental animals, and in the control animals the increase was between 39.2 per cent and 45 per cent. Also within certain limits the animals receiving multiples of the physiologic optimum of iodine showed lower basal metabolic rates and their thyroids were microscopically not active. There was no signified decrease at the end of the lactation period.

In this admittedly small series of rabbits there are findings that are worthy of repetition and discussion. One of the most striking results was the contrast between the increased heat production and the activity of the glands removed at term. In practically every case in which iodine was given, the heat production and oxygen consumption were elevated out of proportion to activity in the thyroid. This was not as evident in those animals receiving little or no iodine. The composite table (Chart II) bears evidence of the above statement, when one examines the 5th and 6th columns, noting the percentage increase of B.M.R. with pregnancy and the activity of the corresponding thyroid. In view of the increased activity of the thyroid and the higher B.M.R. in the control rabbits receiving no iodine, there would seem to be a definite sustaining effect of iodine on the thyroid of rabbits during pregnancy. This may be described as a stabilization of the thyroid activity so that the increased demands may be met without apparent taxation of the gland. If this is true, it does not correspond with the conclusions of Plass and Yoakman (4) who feel that iodine does not prevent gestational hypertrophy but merely aids the abnormal gland. It is of interest to note that the figures of this series correspond to certain clinical reports. The increases of the B.M.R. with pregnancy parallel those reported by Baer (2) and Cornell (3). The increased number of young borne by iodine-fed mothers agrees with the findings of Smith (12). These, however, are minor points. The most evident result is that of the definite influence of iodine on the thyroid gland of rabbits during pregnancy which has been well established clinically for many years and seemingly is substantiated in this report.

CONCLUSIONS

In view of the foregoing results there would appear to be limited but definite evidence that in rabbits iodine has a sustaining effect on the thyroid gland during pregnancy and also probably lowers the metabolic shock incident to the pregnant state. The above assertion is based on the lower basal metabolic rates and less active thyroid glands recorded for the animals receiving iodine daily.

SUMMARY

Clinical and experimental observation indicate that pregnancy incites an increased metabolic rate, although there is some disagreement as to whether or not thyroid function is increased. The administration of iodine and thyroid to pregnant animals is also said to have a beneficial effect upon the young. Such observations as well as the frequent occurrence of fulminating hyperthyroidism in women with histories of repeated pregnancies leads to the suggestion that the repeated excitation of the thyroid gland may eventually result in functional thyroid imbalance and that such imbalance may be in part dependent upon iodine deficiency. In the investigation of this problem 13 healthy female rabbits were selected, fed with standard prepared rabbit food and housed under careful conditions. They were given varying doses of iodine in the form of Lugol's solution. These doses were calculated according to the physiologic optimum (0.045 mgm. for human adult in 24 hours). The rabbits were given amounts varying from 0.00065 mgm. to 0.00305 mgm. or 1, 2, 3, and 4 times the physiologic requirements of iodine. These dosages were maintained throughout the period of pregnancy and lactation. Three of the rabbits (controls) received no iodine. Seven of the ten experimental animals became pregnant, two developed infection and one proved sterile. Two of the controls also became pregnant. From 8 to 25 basal metabolic determinations were made on each rabbit. These indicated that those rabbits given additional iodine developed a smaller (3.6 to 2.9 per cent) increase in the basal metabolic rates than did the controls (39.2 to 45 per cent increase).

The study of microscopic sections of the thyroid glands revealed degrees of activity that corresponded with the basal metabolic rate variation. In those rabbits receiving an increased amount of iodine there was less evidence of functional activity than in the glands of the controls. The inactivity was most pronounced in the thyroid glands of those rabbits receiving four times the physiologic iodine requirement. There was no striking difference in the lobes of the thyroid at the time of delivery of the young and at the end of lactation. There is, therefore, evidence that the increase of the physiologic doses of iodine tends to compensate the metabolic demands of pregnancy and thus protect the thyroid gland from overfunctioning.

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Abstract Department

Three cases of Addison's disease treated with an extract of suprarenal cortex. Benham, H. W., Mary Fisher, I. More, and C. J. L. Thurgar, Lancet, **1**: 125. 1932.

The effect of an extract of the suprarenal cortex on three proved cases of Addison's disease is described. In spite of some temporary benefits of the usual striking nature, there was no permanent relief with the amounts and type of extract used.—R. L. Zwemer.

Effects of cortico-adrenal extract on carbohydrate metabolism in normal animals. Britton, S. W. and H. Silvette, Am. J. Physiol. **100**: 693. 1932.

Extracts of the adrenal cortex of proven potency were found to have a marked influence on carbohydrate metabolism in normal cats, rats and rabbits. Young animals were particularly responsive. In them the blood glucose and liver and muscle glycogen values were considerably elevated within an hour after injection of the extract. Six hours after injection (in rats) the levels were still maintained higher than in controls treated with adrenaline or saline solutions. Storage of glycogen in the liver after extract treatment was enhanced three to five times above that of the controls. Large amounts of dilute adrenaline solution (1:2,000,000), given intraperitoneally to young rats, produced increases in blood sugar and reductions in muscle glycogen. Liver glycogen was also in many cases reduced. The increments in hepatic glycogen produced by the extract form the basis of a relatively simple and economical means of testing the potency of the material.—R. G. H.

Experimental adrenal exhaustion. Edmunds, C. W. and R. G. Smith, J. Lab. & Clin. Med. **17**: 399. 1932.

In a series of controlled experiments it was demonstrated that the epinephrine content of the adrenal glands of dogs was reduced by subcutaneous injection of large doses of physostigmine to approximately one-half within 4-5 hours and to one-third within 24 hours. By 48 hours after injection the glands had largely replenished themselves. (Average of results in mgm. of epinephrine per gm. of fresh gland: Normal—1.51; 4-5 hours—0.73; 24 hours—0.55; 48 hours—1.55.) Physostigmine administered twice daily for some days produced an even greater depletion of the adrenal medulla. The characteristic weakness and apathy of the physostigmine-treated dogs was very profound in such cases. An attempt was made to hasten the recovery of the exhausted glands by administration of possible precursors of epinephrine. In this regard tyrosine apparently had no effect. Dihydroxyphenylalanine gave some evidence of a beneficial action but the results were not conclusive on account of the wide variations in the different animals. Subcutaneous injections of strychnine did not decrease the epinephrine content of the adrenal glands.

—R. G. Smith.

The action of adrenaline on glycogen distribution in the cat. Evans, C. L., C. Tsai and T. G. Young, J. Physiol. **73**: 103. 1931.

Rats were injected subcutaneously with 0.2 mgm. of adrenaline per kgm. of body weight and killed after 3½ to 4 hours. Control animals received an equivalent volume of 0.9% salt solution. Muscle glycogen was decreased, liver glycogen increased. Blood sugar was definitely increased and blood lactate decreased slightly. Subcutaneous injection of similar amounts of adrenaline in cats caused after 5 to 7 hours an insignificant decrease in muscle glycogen and an increase in liver glycogen which the authors do not consider significant. Blood sugar was increased, blood lactate unchanged. Continuous intravenous infusion over 1 to 8 hours of adrenaline from 0.09 to 0.65 mgm. per kgm. in amytalized cats with interval sampling, gave, in 20-30 minutes, a pronounced decrease in glycogen content of both muscle and liver and an increase in blood lactate and sugar; after a longer interval (150-280 min.) there was a tendency to recovery of all factors. Similar experiments on decapitated and

decerebrated cats gave similar results except that there was no tendency to recovery in 5 hours when the infusion was discontinued after an hour. Five hours after discontinuance of infusion there was a tendency to recovery.

—C. I. R.

Irradiation therapy in functional ovarian disorders. Ford, F. A., Radiology, **16:** 936. 1932. Abst., Am. J. M. Sc. **184:** 132.

During the past few years there have been several references in the literature to the possibility of stimulating the function of the ovary in cases where this function is depressed by the employment of small doses of Roentgen ray irradiation and on the whole the reports have been of a favorable nature. In the Mayo Clinic 47 cases were treated with Roentgen ray for habitual amenorrhea or oligomenorrhea or sterility associated with these conditions and 29 cases were treated for dysmenorrhea. The dosage employed was approximately 5 to 10% of an erythema dose. Of the 47 cases treated for amenorrhea, ranging in age from 19 to 37 years, 36 were irradiated over the ovary, 5 over the pituitary and in 6 there was combined treatment of both ovary and pituitary. The report of the results is not available in 6 patients, 15 failed to react, while in the remaining 26 cases menstruation was re-established within 6 weeks after the treatment and has continued regularly in the majority of patients for periods varying from a few months to 2 years. Seven pregnancies have occurred among 6 of the 24 married patients, all of whom had previously been sterile. Of the 29 cases of severe dysmenorrhea, relief of pain followed the irradiation in 18. Although the duration of relief is extremely variable, by repeated irradiation a satisfactory result has been obtained as long as 3½ years in one case. Evidence has not been found that repetition of treatments at intervals of 3 months or longer has adversely influenced ovarian function.

Blood calcium regulation in man. IV. Action of adrenaline, atropine and pilocarpine (Die Blutkalkregulation im menschlichen Organismus; die Wirkung von Adrenalin, Atropin und Pilokarpin). Hetényi, G. and A. Gaál, Ztschr. f. d. ges. exper. Med. **75:** 516. 1931. Abst., Chem. Absts. **26:** 1658.

Of the vegetative nervous system stimulants only adrenaline has a definite action. It lowers the blood calcium.

The effect of complete suprarenalectomy on the oestrual cycle of the white rat with reference to suprarenal-pituitary relationship. Martin, S. J., Am. J. Physiol. **100:** 180. 1932.

Complete suprarenalectomy in female white rats resulted in 88% of the cases in a suppression or irregular appearance of the oestrual cycle. In females, 80.1% died from double suprarenalectomy. Intra-ovarial transplants of suprarenal cortex maintained normal health and body weight and restored normal ovarian activity. Complete suprarenalectomy in adult females, normal and castrate males, changed the cytological picture of the hypophysis and produced a marked decrease in the gonad stimulating hormone of the anterior lobe. Subcutaneous injections of theelin and of extracts of gonad stimulating hormone of the anterior hypophysis were effective in restoring oestrum although the females died from suprarenal insufficiency. Similar injections of normal saline and epinephrine chloride gave negative results. The ovarian disturbance following complete suprarenalectomy was not due to operative trauma, avitaminosis (A, B, D, E) or to the gradual loss in body weight not exceeding 21%. In view of the inconsistent and varied effect on the ovary following double suprarenalectomy and the functional and cytological changes of the anterior lobe always coincident with marked ovarian disturbance, it is believed that an intermediate factor is present. This has been found to be the hypophysis and serves to explain the mechanism involved in the oestrual disturbance.

—R. G. H.

Suprarenal tumor with metastases. Peterman, M. G., Am. J. Dis. Child. **43:** 655. 1932.

A case is reported, with autopsy findings, of a boy three years of age with Hutchinson's syndrome due to sarcoma of the adrenal medulla with metastases in the skull and sacrum. The boy also presented a left facial paralysis.

—M. B. G.

The relation of the adrenals to the carbohydrate metabolism of the musculature (Beziehungen der Nebenniere zum Kohlehydratstoffwechsel der Muskulatur). Roese, H. F., Ztschr. f. d. ges. exper. Med. **78**: 426. 1931. Abst., Chem. Absts **26**: 1329.

An adrenal-extremity preparation with artificial circulation utilizes sugar at the same rate as a simple extremity preparation. The usual increase in muscle glycogen is not seen, and lactic acid is given off by the muscles. The intact adrenal has the same effect on carbohydrate metabolism as adrenaline. There is no basis for the belief that the cortical hormone, perhaps choline, is antagonistic to adrenaline.

Suprarenal hemorrhage in the new-born infant. Rosenblum, J., Am. J. Dis. Child. **43**: 663. 1932.

A case is reported of an infant presenting high temperature, rapid respirations, palpable abdominal tumor, hypoglycemia and nitrogen retention. The child recovered.—M. B. G.

Excretion of enzymes after injection of thyroxine, adrenaline and insulin (Über das Auftreten von Proteasen im Blut bzw. Harn nach parenteraler Zufuhr von Thyroxin, Adrenalin und Insulin). Abderhalden, E. and E. Wertheimer, Fermentforsch. **12**: 421. 1931. Abst., Physiol. Absts. **16**: 270.

It has already been reported that injection of pituitary or ovarian hormones leads to the appearance of specific enzymes in the urine. Similarly, injection of thyroxine, adrenaline, or insulin in small amounts leads to the excretion of enzymes specific for thyroid, suprarenal, and pancreas substrates respectively. The former is effective even in thyroidectomized animals.

The etiology of mongolian idiocy on the basis of reports in twins (Über die Atiologie des Mongolismus anhand der bisherigen Ergebnisse der Zwillingserforschung). Bauer, A., Arch. f. Kinderh. **90**: 169. 1930.

The author analyzed 44 reports from the literature and one of his own, in which mongolianism occurred in twins. In 32 cases, only one child was mongoloid; in 17 cases of dizygotic twins of different sex there were 11 males and 6 females; in 7 dizygotic twins of the same sex, two were males and five females; in 8 twins of the same sex, uncertain as to one or two egg, there were 4 males and 4 females. In 6 cases both twins were mongoloid and of the same sex; 3 were males and 3 females. There were 6 doubtful cases. The author believes that the condition is due to germinal factors and not to exogenous conditions of the mother during pregnancy.—M. B.

Hibernation of thirteen-lined ground squirrel Citellus tridecemlineatus (Mitchill); influence of thyroxin, pituitrin and desiccated thymus and thyroid on hibernation. Johnson, G. E. and V. B. Hanawalt, Am. Naturalist, **64**: 272. 1930.

The feeding of desiccated thymus and thyroid in large doses to 27 and 23 animals, respectively, resulted in no definite increase or decrease in tendency of grown squirrels to hibernate when subjected to cold temperatures. The injection of thyroxine and pituitrine in doses which were, respectively, 225 and 450 times the human dose on the basis of relative weights, produced no change in tendency to hibernate in 66 and 116 animals, respectively, in comparison with the same number of controls. The animals were subjected to cold temperatures after the injections. The experiments indicate that the secretions of the thymus, thyroid and posterior pituitary are not important agents in the production or prevention of hibernation.—Authors' Summary.

The chemistry of the growth substance. Kogl, F. and A. J. Haagen Smit, Proc. Acad. Sc. Amsterdam, **34**: 1411. 1931. Abst., Chem. Absts. **26**: 2755.

The hormone controlling the elongation of plant cells was found to be present in cultures of B. coli, Rhizopus species and yeast, and also in large amounts in human male or female urine. The $NaHCO_3$-solution fraction of the Et_2O extract of pregnant urine was thoroughly extracted with petroleum ether and with benzene, and the insoluble residue converted to a Pb salt which was

fractionally precipitated with EtOH. By acidifying the extract with Et_2O a concentrate in which one plant unit weighed 10^{-6} mgm. was obtained. Treatment of this with 1% HCl in MeOH converted the growth substance to a form, probably a lactone, in which it was no longer soluble in alkali. Distillation of this compound in vacuo gave a fraction, b0.1 about 125°, from which active crystals, melting at 172°, were obtained. One plant unit of this substance, for which the name auxine is suggested, weighed only 3.3×10^{-9} mgm. The molecular weight was about 340, agreeing with that found by Went, and formula approximately $C_{18}H_{32}O_4$. Commercial preparations of female sexual hormone contained the growth substance as impurity, but crystalline theelin was inactive.

Relationship of bartonella anemia and spleen hormone. Koh, M. J. Chosen M. A. **22**: (No. 6). 1932.

The author observed that splenectomy in rats was usually followed within three to five days by evidences of multiplication of Bartonella muris in the blood stream. The transplantation of splenic tissue or subcutaneous injection of extract of desiccated spleen was followed within two or three days by disappearance of infection. Serum from the splenic vein of normal rabbits or dogs had a similar protective effect. Irradiating the donor with a quartz lamp was found to double the titre of the protective substance. This substance which the author regards as a specific splenic hormone was found to be soluble in water but not in alcohol or ether. It resisted heating at 80° for 30 minutes but was destroyed quickly at 100°.—Condensed from Author's Abst.—R. G. H.

Pathogenesis of lipodystrophy. Masloff, E. V., Medizin. **6**: 1. 1931.

Many authors have studied the connection between lipodystrophy and lesion of the central nervous system. Two forms of lipodystrophy are recognized: the classic or full form in which there is simultaneously upper atrophy and lower hypertrophy and a partial form in which there is only atrophy or hypertrophy. The case observed by the author belongs to the partial lower lipodystrophy described by Viard and Laignel-Lavastine. The beginning of the adiposity coincided with infection of chronic epidemic encephalitis. It is probable that in this case there was a lesion of the supracervical nuclei and of the hypothalamic region.—M. Breitmann.

Blood sugar and the thymus-adrenal medulla antagonism (Blutzucker und Thymus-Nebennierenmark-Antagonismus). Messini, M., Arch. f. exper. Path. u. Pharmakol. **161**: 247. 1931. Abst., Chem. Absts. **26**: 1339.

Subcutaneous injections of thymus extract into rabbits cause a slight hyperglucemia within several hours, accompanied by a decrease in serum inorganic phosphorus. Adrenaline (1 mgm. per kgm.) injected during this hyperglucemia causes an additional rise in blood sugar, comparable to that obtained in the normal animal. Thymus extract injected simultaneously with adrenaline inhibits the adrenaline hyperglucemia and glucosuria. The significance of these findings is discussed. There is an extensive bibliography relating to the possible rôle of the thymus in carbohydrate metabolism.

The effect of extracts from the thyroid, mammary and ovary glands on the isolated rabbit intestine (Über die Wirkung der Extrakte aus Schild-, Brust-, u. Ovarialdrüsen auf den Isolierten Kaninchendarm). Tutajew, G. W., Ztschr. f. Biol. **91**: 496. 1931. Abst., Chem. Absts. **26**: 1651.

These glands stimulate the activity of the intestine. The mammary glands call forth a strengthening of the to-and-fro peristalsis movements and a slowing of the "rhythmus" without affecting the tonus. The ovarian extracts strengthen the latter also. Thyroid extract acts similarly except that small doses effect a weakening in peristalsis.

Obesity and its treatment. Tuszewski, S., Nowiny Lakarskie, Poznan. **43**: 736. 1931. Abst., J. A. M. A. **98**: 1235.

Tuszewski discusses the present status of obesity, especially its treatment. He calls attention to the water retention action of the pancreas noted in connection with insulin treatment. After a discussion of causes, diet, habits and

endocrine glands, he summarizes the treatment into dietetic, glandular and physical therapy. With regard to the diet, he believes that from 100 to 150 grams of albumin is a daily requisite to maintain proper metabolism. Fats and sugars are to be excluded, especially sugars, which, in his opinion, promote absorption of foodstuffs. The views on water are interesting: far-reaching restriction of liquids is advised, and the same in reference to table salt (to remove water retention). Diuresis is strongly advised. The glandular therapy is restricted to the thyroid (to increase metabolism), anterior pituitary and sex glands, and this mode of treatment is essential in obesity. Exercise is a valuable adjunct but the condition of the heart should be watched; all cases of obesity present some injury of the heart or circulation. Massage, as well as hot baths, he holds to be worthless; cool baths (15° C.) are beneficial. The diaphoresis should be replaced by diuresis to avoid discomfort.

Metabolic changes and treatment of obesity. Wohl, M. G., Am. J. M. Sc. **183**: 613. 1932.

Studies were made upon the basal metabolic rate, the specific dynamic action and the water and salt retention in persons suffering from obesity. No constant relationship was discovered between the metabolic rate and the excessive deposition of fat. In a certain group of hypothyroid patients, four of seven were underweight. A low basal rate is therefore considered of no great moment in the pathogensis of obesity. The specific dynamic action estimated 45 and 90 minutes after the ingestion of a given meal did not vary greatly from the normal. Water and salt retention may account for failure to reduce some persons on the ordinary reduction regime. Studies of the Volhard water test and of the McClure-Aldrich intradermal salt solution test in seven cases of obesity showed a definite diminution of urinary output and a rapid absorption of salt in five. The venous and capillary NaCl estimations two hours after administration of 10 gms. of NaCl by mouth were inconclusive, but it is noteworthy that two patients who showed retention of NaCl have lost considerable weight under a salt restriction and dehydration regime. Salyrgan intravenously, as a dehydrant, was employed with apparent success.—E. K. Shelton.

Observations on the assay of the comb-growth promoting hormone. Blyth, J. S. S., E. C. Dodds and E. J. Gallimore, J. Physiol. **73**: 136. 1931.

An investigation as to whether there is a quantitative relationship between the amount of material injected and the response of the animal to a given stimulus. Nineteen Brown Leghorn capons were castrated at 3 to 78 days of age. Comb measurement were made fortnightly. Daily injections over 10 days were made of 0.3 cc. of an active preparation from male urine. Injection periods were 6 weeks apart. Average growth ratios graded from 1:6 after the first two periods to 1:2 at the end. This demonstrates the variability of responses of different birds and hence the necessity of assay by statistical methods, using a large number of birds.—C. I. R.

Further clinical studies of the anterior pituitary-like hormone of the human placenta. Campbell, A. D. and J. B. Collip, Canad. M. A. J. **25**: 9. 1931.

The authors give the following impressions of their detailed study of 40 cases: In menorrhagia of the simpler types, treatment with anterior-pituitary-like hormone for one week before the epoch materially reduces the flow. Menorrhagia of the more severe type may require treatment for three months or more before normal periods are established. In metrorrhagia, when the continuous uterine bleeding has been in a measure controlled, the same tendency to the establishment of normal cycles as in the menorrhagia groups has not been observed. Also, intervals of amenorrhoea may appear in such cases. No enlargement or engorgement of the breast has been observed in any of the cases of this series. The histological picture of the endometrium obtained by curetting is not necessarily a reflection of the clinical symptoms.—A. T. C.

The clinical importance of the sex hormones. Dodds, E. C., Am. J. Obst. & Gynec. **22**: 520. 1931.

The author reviews the literature, and pays special attention to the following points: (1) The difficulty of standardization in view of recent work showing that oestrus response depends upon the refractoriness of the animal,

the mode of administration—whether oral or subcutaneous—the purity of the material, and the type of vehicle in which it is dissolved, e.g., oil or water. (2) The purity of the substance bears a direct relationship to the amount which has to be given to produce oestrus by mouth, the crude material being much more active than the highly purified. Clinical experiments with the oestrus-producing hormone are described, and the importance of giving very large doses is emphasized. The paper concludes with an account of the Aschheim-Zondek reaction for pregnancy. The author indicates in what direction further developments are to be expected and emphasizes the important part which the sex hormones will play in clinical medicine.—Author's Abst.

The excretion of estrin during pregnancy. Edwards, Dorothy, Am. J. Obst. & Gynec. **231**: 694. 1932.

Since estrin has been so widely found in the excretory products of the human body and in larger quantities during pregnancy it was decided to attempt to extract it from saliva and gastric juice of pregnant women. Samples of saliva were taken from patients, toxic and non-toxic, during different stages of pregnancy. The method of assay used was the vaginal smear test of Allen and Doisy. Three ovariectomized mature rats were used for each sample. Single subcutaneous injections were made in each case and the vaginal smears were read approximately forty hours and forty-eight hours after injection. The samples of saliva all gave negative results. The chemical procedure and assay were checked by using urine and saliva collected from the same patient. Ten patients were selected, all of them past the seventh month of pregnancy. The urine in all cases was positive for the presence of estrin while the saliva was negative. Three patients in the last month of pregnancy were made alkaline by administering sodium bicarbonate. The urine (alkaline) of these patients contained estrin but it was not present in the saliva of the same patients. After assaying different dilutions of theelin, a known amount of theelin was mixed with a known quantity of saliva and when the mixture was assayed all smears were positive which showed that the female sex hormone is not destroyed by saliva. Gastric juice was collected from three patients at term and was subjected to the same procedure as was used in extracting estrin from urine and was found not to contain estrin. It was concluded that estrin is not excreted from the alimentary canal above the duodenum in large enough quantities to produce the typical cornification of the vaginal mucosa.
—Author's Abst.

Treatment of hemophilia by an ovarian extract by Birch's method. Foord, A. G. and B. R. Dysart, J. A. M. A. **98**: 1444. 1932.

A subject of clinical hemophilia actively bleeding following tonsillectomy was treated by one injection of an ovarian extract, with prompt stopping of bleeding. The response may have been non-specific or a coincident, but in view of Birch's similar results further trial of this type of therapy to evaluate the method properly is recommended.—R. G. H.

Mating instincts in spayed rats with transplanted ovaries. Hemmingsen, A. M., Skandinav. Arch. f. Physiol. **63**: 87. 1931.

Various degrees of intensity of the mating behavior of female rats have been observed. Highest intensities were observed at night. Between 9-12 p.m. sexual excitement of the female often was aroused by mechanical stimulation of the back or tail in the absence of a male. All degrees of sexual excitement were observed in spayed rats with transplanted ovaries.—E. L.

On the mechanism of certain ovarian hormonal influences on the central nervous system. Herren, R. Y. and H. O. Haterius, Am. J. Physiol. **100**: 533. 1932.

Ten rats bilaterally sympathectomized from the level of the renal arteries through the pelvis (including the pelvic nerve) did not show the correspondence between oestrus and lengthened Achilles reflex time that is exhibited by normal animals. Bilateral abdominal sympathectomy did not alter the length of the normal oestrous cycle. From results obtained, it seems highly probable to the authors that certain influences of the ovarian hormones on the higher nervous levels are effected through the sympathetic connections and are not in the nature of direct stimuli.—R. G. H.

Ovarian substance influencing metabolism (Untersuchungen über einen Stoffwechselwirksamen Extrakt des Ovariums). Kaulmann, C., C. Müller and O. Mühlbock, Klin. Wchnschr. **11:** 14. 1932. Abst., Physiol. Absts. **17:** 210.

An extract of Graafian follicles, free from folliculin, causes increase in the rate of metamorphosis in tadpoles and retards growth. The extract is active in 1 in 100 dilution. Extracts of the whole ovary were inactive.

Pseudo-hermaphroditism and the interstitial cells (Pseudo-hermaphroditismus und die Zwischenzellen). Orsos, E., Deutsche Ztschr. f. Chir. **230:** 211. 1931. Abst., Biol. Absts. **6:** 1633.

In an otherwise intensely feminine woman, operation revealed the total absence of ovaries and uterus. Each groin contained a mobile structure the size of a nut, histological examination of which revealed an abundance of interstitial cells. The author concluded that these cells have no influence on the secondary sexual characteristics.

The action of ovary-stimulating substance of human urine of pregnancy on uterine motility in the unanesthetized rabbit. Reynolds, S. R. M., Am. J. Physiol. **100:** 545. 1932.

It was found that as little as 0.05 cc. of the ovary stimulating substance of human urine of pregnancy induces a transitory decrease in the motility of the uterus of the unanesthetized rabbit, in six to eight hours. When the ovary is present only excessive follicular growth results from such a small dosage of the urine-substance. Larger amounts (0.4-1.0 cc.) in the presence of the ovary induce lasting uterine quiescence and at the same time, ovulation. With such amounts, a similar response has been demonstrated in suitable castrated rabbits. One may conclude that the effect of the urine-substance is independent of the ovary, yet when this organ is present it probably contributes to the effect.—Author's Abst.

Further observations upon the experimental production of ovulation in the rabbit. Snyder, F. F. and G. B. Wislocki, Bull. Johns Hopkins Hosp. **49:** 103. 1931.

Following intravenous injection, the active substance of concentrated human urine of pregnancy that causes ovulation in the rabbit can be recovered from rabbit's urine. The active substance causing ovulation in the rabbit disappears from human urine within several days following removal of the pregnant uterus. An active substance causing ovulation in the rabbit has been found in human amniotic fluid and extracts of the anterior lobe of cattle. Negative findings have been obtained with human cerebrospinal fluid and human placental implants, as well as with various substances from other mammals. Ovulation in the rabbit occurs after a smaller dose of concentrated human urine of pregnancy given intravenously than when given subcutaneously or intraperitoneally. In immature rabbits, prior to the fourth month, a single intravenous injection of concentrated urine of pregnancy produces no visible macroscopic change in the ovaries. Beginning with the fourth month a striking change occurs in the ovaries following injection of concentrated urine or anterior lobe extract. This response in immature animals is characterized by the occurrence of edema, hemorrhage and blood follicles. In the pregnant rabbits, ovulation can be induced throughout pregnancy by the injection of concentrated human urine of pregnancy. There is a tendency towards inhibition of ovulation especially during the first four days of gestation. In the cat, ovulation does not occur in the range of dosage of concentrated human urine which induces ovulation in the rabbit.—Authors' Summary.

The action of anterior lobe pituitary extract and thyroid extract upon the formation and growth of tumors caused by tar (L'action des extraits tires du lobe antérieur de l'hypophyse et de la glande thyroïde dur la formation et le développement des tumeurs obtenues par l'application de goudron). Sciesinski, M. C., Compt. rend Mensuels de la Classe de Med. (No. 7-8), 1. 1931.

The author, using rabbits which had been treated with tar to cause the growth of tumors, injected anterior lobe pituitary extract subcutaneously into 8 rabbits and thyroid gland extract into 9 rabbits with the following results.

The tumors caused by the tar made their appearance earlier in the pituitary injected rabbits, the limits being 22-36 days, with an average of 28 days. The control rabbits had tumors in 19-67 days with an average of 38 days. The animals receiving subcutaneous injections of thyroid extract developed tumors at about the same time as their controls, between 18-54 days with an average of 38 days. Neither the pituitary nor thyroid extracts had any effect upon the development and size of the tumors. The pituitary and thyroid gland extracts neither increased nor stopped the growth of the tumors. In the groups receiving the extracts as well as in the control animals the rapid growth of the tumors with persisting metastases could be observed. The action of the extracts together with that of the tar was evident. Control animals, untreated with tar, showed no results from extract injections.—J. Gagnon.

Theelin. Some physical and chemical properties. Thayer, S. A., L. Levin and S. A. Doisy, J. Biol. Chem. **91**: 791. 1931.

Theelin is a keto monoatomic alcohol having a formula $C_{18}H_{21}O(OH)$. Acetylation gives a monoacetyl derivative having a melting point of 125.3° (uncorr.). Theelin can be recovered by hydrolysis of the ester. Methylation produces a monomethyl ether melting at 165° (uncorr.). An oxime was prepared melting with decomposition at 229° (uncorr.). Theelin contains one double bond that adds iodine. It melts at 254-257° (corr.). Probably the higher temperature is correct for theelin. Theelin is dextrorotatory.

—Authors' Abst.

Symptoms accompanying ovarian hypofunction. Werner, A. A., J. Missouri M. A. **28**: 363. 1931.

The author presents a study of the incidence of various sorts of symptoms in 40 women deprived of their ovaries and 96 in the menopause. The symptomatology was quite similar in the two groups. Order of frequency of symptoms (per cent): Menstrual disturbances, 98.9; nervousness subjective, 96.3; hot flashes, 92.1; excitability, 76.5; fatigability, lassitude, 76.5; constipation, 72.7; vertigo, 70.9; irritability, 64.4; depression, crying, 61.8; sleep disturbed, 61.9; tachycardia, palpitation, dyspnea, 60.2; decreased memory, concentration, 53.3; scotomata, 45.0; occipitocervical pain, 43.8; headache, 37.5; cold hands and feet, 30.7; numbness, tingling, 27.1; psychosis, 26.7; formication, 23.2; vague pains, not recorded. This group of symptoms is designated "menopausal syndrome." It is suggested that certain cases of neurasthenia actually represent ovarian deficiency that is amenable to appropriate glandular treatment. It is assumed that the symptomatology is in part due to secondary disturbance of the function of the thyroid and adrenals.—R. G. H.

Studies on hypophysis hormones; influence of pituitary hormones on the germination of seeds of Lupinus albus L. Agnoli, R. T., J. Pharmacol. & Exper. Therap. **44**: 55. 1932.

The author reviews the literature on the use of growing plant tissues for the detection of activity of organic substances such as toxins and hormones. This work has been somewhat extensively prosecuted in Italy since 1896, though the first report of the use of Lupinus albus was made by Kohlenberg and True in 1896. Agnoli tested the effects of thyroxine, aqueous extract of thymus and various pituitary preparations. The two first mentioned were found to have no effect but an alcohol-ether (lipoidal) extract of pituitary gland, personally prepared, definitely promoted growth. Of other pituitary derivations "Prolan" and "Praephyson" were also without effect. Organic nitrogen, as such—e.g., urea, was also ineffective.—R. G. H.

The intraglandular cleft of the pituitary body and its connections. Brander, J., J. Anat. **66**: 203. 1932.

Serial sections of human hypophysis (and of some animals, number involved not stated) indicate to the author that there is a patent opening from the intercavernous blood sinuses of the dura (surrounding the hypophysis) and the lower pole of the residual lumen or intraglandular cleft; thus permitting masses of colloid to pass as such directly from the cleft to the venous blood stream. The author admits that the introduction of masses of colloid

directly into the blood stream introduces a novel physiological conception. There is some discussion and illustrations of the blood vessels to the hypophysis. The presence of a subarachnoid space about the hypophysis is denied.
—A. T. R.

Further notes on pituitary basophilism. Cushing, H., J. A. M. A. **99**: 281. 1933. Abst., A. M. A.

In a recent paper the author reported 12 examples of a peculiar and clinically unmistakable polyglandular syndrome. The disorder is characterized by a rapidly acquired plethoric adiposity affecting the face, neck and trunk, the extremities being spared. It is associated in women with hypertrichosis and amenorrhea. Other characteristic features are vascular hypertension, purplish striae distensae of the abdomen, and acrocyanosis with cutis marmorata of the extremities. It is often accompanied by hyperglycemia, occasionally by polycythemia, and a peculiar softening of the bones of the skeleton has been commonly found at autopsy. In its extreme forms, the malady has more often been encountered in young adults, and the average duration of life in the fatal cases has been something over five years. It is not an uncommon syndrome. Numerous typical examples have been reported, the disease in most instances having been ascribed to a primary suprarenal disorder for the reason that cortical hyperplasia is a not uncommon postmortem observation. However, in five of the eight cases that had come to autopsy an unsuspected pituitary adenoma was found; and the fact that three of them were unmistakably composed of basophilic elements made it probable, in view of the supposed rarity of adenomas of this type, that the pituitary lesion was the primary cause of the syndrome. This at least was the interpretation put on the matter, the symptomatic evidences of disordered function of suprarenal cortex, of pancreatic islets, of parathyroid glandules and of reproductive glands being looked on as wholly secondary expressions of the general endocrine derangement. Since the publication of the preceding paper, new facts have come to hand which seem further to strengthen the views therein expressed. Additional cases serve to increase the percentage of proved basophil adenomas in association with the polyglandular syndrome under discussion. Instead of only three out of eight cases that had been examined post mortem, there are now six out of 11 in which a pituitary basophil adenoma has been disclosed. The pituitary body in two other cases was said to be normal, but in the absence of serial sections this mere statement is no longer convincing. When one takes into consideration not only the presumed infrequency of adenomas of this type but their small size, whereby they easily escape detection, and couples this with the fact that chief attention has been paid to the condition of the suprarenal glands in all the autopsies heretofore conducted, the fact that a basophil adenoma has been found in half of the patients who have succumbed to this peculiarly unmistakable malady must be something more than coincidence.

The anterior pituitary sex hormone in the blood and urine of rats. Emery, F. E., Am. J. Physiol. **101**: 246. 1932.

The amount of anterior pituitary sex hormones in the blood and urine of several types of rat donors was tested by injecting immature female rats. Positive results, as represented by enlargement of the ovaries and uterus and signs of oestrus, were obtained with castrated male and castrated female sera (20 cases). The hormone was not found in serum of normal males, normal females, multiparous or pregnant females (29 cases). Tests with urine collected from normal males, 10 castrated males, 10 castrated females and 8 pregnant rats were all negative. Extracts made from urine were likewise negative.
—R. G. H.

Thymophysin and weak pituitary extract. Comparison in forty cases. Greenhill, J. P., J. A. M. A. **98**: 1260. 1932. Abst., A. M. A.

The author compares the results he obtained in 17 women in the first stage of labor and with weak and infrequent pains or uterine atony by the use of Thymophysin and in 23 others by the use of 25% U. S. P. pituitary extract. The general impressions obtained from the study were as follows: The results in the two series seemed to be almost identical; that is, both Thymophysin and 25% U. S. P. pituitary extract when used in 3 minim (0.2 cc.) doses in cases of uterine atony (not uterine exhaustion) in the first stage of real labor practically always stimulate uterine contractions and in many cases consider-

ably shorten labor. With both preparations there is a tendency to an increase in the patient's blood pressure, but this appears to be more striking after Thymophysin. Hence it is best to avoid the use of these drugs in patients who have marked hypertension. The character of the dilatation of the cervix seems to differ with the two drugs. After the use of Thymophysin it was observed that the cervix usually becomes effaced before it dilates, whereas after the pituitary extract, dilatation and effacement seem to occur simultaneously. On the basis of his observations the author draws the following conclusions: 1. No preparation containing pituitary substance should ever be given as a routine or indiscriminately to shorten labor. 2. No pituitary preparation should be administered in the second stage of labor except on rare occasions. 3. Weak pituitary solution and Thymophysin are seldom effective for the induction of labor. 4. Both 25% U. S. P. pituitary extract and Thymophysin shorten labor in some cases when administered during the first stage of labor. 5. If these substances are used during the first stage of labor they should be given only for a definite indication; namely, uterine atony or some urgent reason for shortening labor; and only small doses should be given; namely, 3 minims or less. 6. The 25% U. S. P. pituitary extract and Thymophysin seem to give almost the same clinical results. The claims of Temesváry for the clinical value of thymus extract in combination with pituitary have not been borne out. 7. The addition of thymus to pituitary extract does not add any factor of safety to the use of pituitary. The clinical use of pituitary extract depends not on the preparation used but on sound clinical judgment, time of administration, dosage and close observance of the behavior of the patient. 8. Occasionally, weak pituitary extract and Thymophysin even in small doses may do harm. Both have a tendency to increase the blood pressure; but may result in incomplete relaxation of the uterus between pains, and both may produce irregularities in the fetal heart rate which even if temporary may nevertheless result in injury to a baby.

The influence exerted by the hormones of the anterior lobe of the hypophysis, the urine of pregnant women, and placental extracts upon the development of sarcomas grafted upon mice (L'action exercée sur le développement de sarcomes greffés sur des souris par les hormones du lobe antérieur de l'hypophyse, par l'urine de femmes enceintes et par des extraits du placenta). Gross, M. L., Compt. rend. Mensuels de la Classe de Med. (No. 718). 6. 1931.

The author has studied the effect of subcutaneous injections of urine, especially urine of pregnant women, upon the development of sarcomas grafted upon white mice. He has also observed the effect of human placental extracts of both early and late periods of gestation, bovine placental extracts and the sexual hormone of the anterior lobe of the pituitary, upon the growth of these tumors. Three hundred and twenty-one white mice have been used in these experiments without conclusive results. However, it appears that the injection of urine of pregnant women and of women afflicted with cancer hastens the development of the sarcoma grafted in the mouse and involves the formation of metastases. This happens 3 to 4 times more frequently in injected animals than in controls. This is not a specific action, since injections of male urine are also followed by an increased growth of the neoplasm, although less pronounced. The injection of urine from a healthy non-pregnant woman increases the frequency of the metastases, so that they are greater than in control animals. The increase in the development of the sarcomas was only very slightly increased by the injection of hypophyseal sex hormone, which had been purified of albuminous substances. The tumors seemed to develop a little more slowly in animals with pieces of human or bovine placenta grafted into them.

—J. Gagnon.

Effects of prolonged oral administration of large doses of pituitary anterior lobe to laying hens. Gutowska, M. S., Quart. J. Exper. Physiol. **21**: 197. 1931. Abst., Chem. Absts. **26**: 1337.

The oral administration of 0.5-0.8 gms. pituitary anterior lobe for a period of 1 month to domestic fowls resulted in increase in egg size and number, weight of birds, and in number and size of follicles in the ovary, stimulation of albumin secretion in the oviduct and also probably an effect on the muscular wall of the uterus.

Action of anterior pituitary upon the thyroid (Die Wirkung des Hypophysenvorderlappens auf die Schilddrüse). Janssen, S. and A. Loeser, Arch. f. exper. Path. u. Pharmakol. **163:** 517. 1931.

Guinea pigs and dogs were injected with beef anterior pituitary as acetone-dried powder suspended in physiological salt solution. Specific effects upon the thyroid were noted: growth of follicular epithelium, vacuole formation and disappearance of stainable colloid. Positive results were obtained in castrated animals showing that the effect is not dependent upon the gonads. No effects followed injection of liver, muscle extract or inactivated anterior pituitary. The thyroid was not affected by oral administration of pituitary although gonad stimulation is recorded. Thus it is concluded that thyroid activation and gonad stimulation are independent effects of the anterior pituitary. Preparations made from the urine of pregnant women did not affect the thyroid of guinea pigs.—W. J. A.

The occurrence of pituitary hormones in the urine in conditions unassociated with pregnancy. Jeffcoate, T. N. A., Lancet, **1:** 662. 1931.

Tests for prolan A and prolan B were made on 169 patients with the following results: The urines of six women at the menopause were examined for prolan A. Three of these contained the hormone. The author believes the functioning ovary inhibits activity of the anterior lobe of the pituitary. Two of the four patients under the menopause age who had a bilateral oöphorectomy without an ovarian graft showed prolan A in urine after operation. In three patients who had bilateral oöphorectomy after the menopause, no prolan A was found in the urine. In urines of two rabbits in a series of five in which the ovaries were removed, prolan A was found. In nine cases of exophthalmic goiter in which five-sixths of the gland was removed, three definitely and two doubtfully, excreted a hormone similar to that of prolan A. The urines of nine patients with benign neoplasms were negative when tested for prolan A. Prolan A was found only once in patients with extra-genital carcinoma but it usually was found when there was a carcinoma of genitalia. Tests for prolan A on the urines of eight rabbits with Brown-Pearce tumors were negative. The author believes the presence of a growth in the genitalia gives rise to impulses which pass from the genitalia to the pituitary.—E. L.

The effects of daily injections of bovine anterior pituitary extract upon developing albino rat. Johnson, G. E. and E. D. Sayles, Physiol. Zoöl. **2:** 285. 1929.

Daily injections of bovine anterior pituitary extract accelerated the growth-rate of young rats. Experimental female rats did not cease their rate of rapid growth as early as did their controls. Treated rats of each sex were significantly heavier (males only slightly so) but did not have significantly longer bones than saline-injected litter-mate controls of the same sex at 150 days of age. Increase in weight was due to general growth and also to marked increase in muscular and visceral development. The extract produced no change in the uterus or in the time of opening of the vagina but reduced fertility of the females and produced an increased size of the ovaries, owing to the development of a larger number of corpora lutea. Some follicles and several corpora lutea contained degenerating ova. The development in the size of the testes was not affected by the injections of the extract. Extracts prepared from glands which had been chilled for 24 hours were potent, as they affected the body growth and the sex organs of the treated animals.—Authors' Summary.

The Aschheim-Zondek pregnancy test, its clinical application in a series of cases. Jones, R. H. and E. R. Mugrage, Am. J. Clin. Path. **1:** 379. 1931.

The test has given this laboratory a very satisfactory means for the differential diagnosis of early pregnancy, since the low percentage of error ranks it with the most accurate of laboratory procedures. In many cases very definite and valuable aid has been given the clinician in the diagnosis of the presence or absence of pregnancy at a time when the clinical signs were of little or no help. The use of rats in place of mice has proven very satisfactory, for several reasons. The rats are larger, mature later, and so can be used when older and better able to withstand infection. The mortality in these test ani-

mals is practically nil as compared with the large number lost when mice are used. It is also much easier to handle the larger animals, and to read the results macroscopically. Toluol as a preservative of the urinary specimens has proven very satisfactory, since it in no way affects the hormone content of the urine and does keep down the bacterial contamination. By its use specimens may be sent from a considerable distance, and run at a central laboratory. Specimens a week to ten days old preserved with toluol have been tested and have given accurate results. The results as obtained by the procedure used in this series have failed to show any material difference in the quantity of hormone early or late in pregnancy. They do show that the hormone is demonstrable very early in pregnancy, which makes the test satisfactory as an early diagnostic aid. Modifications with the use of rabbits offer a shortened time interval, but for routine tests white rats have proved more economical, require less technical skill, and the time element, with rare exceptions, has been negligible.—Authors' Summary.

Antagonism of menformon and hormone of anterior lobe of pituitary (L'antagonisme de la menformone et de l'hormone du lobe anterieur de l'hypophyse; experiences sur des animaux steriles). Laqueur, E. and S. E. de Jongh, Arch. neerl. de physiol. **16**: 286. 1931. Abst., Physiol. Absts. **17**: 63.

The hormone of the anterior lobe of the pituitary gland can overpower the inhibiting action of menformon upon testicular secretion in rats and mice (shown by decrease in the weight of the seminal vesicles); similarly large doses of menformon can partially overpower the stimulating effect of the pituitary (shown by increase in weight of the vesicles). The latter produces slight testicular hypertrophy only, but the vesicles increase in weight 30 times; however, it prevents the testicular atrophy produced by menformon. The two secretions are also antagonistic in their effect on Leydig's cells. In senile rats 2½ to 3 units of anterior pituitary hormone injected daily for 15 days produced increase in size of the testes and seminal vesicles.

Influence of posterior pituitary extracts on mineral and water exchange in children. Manchester, R. C., Proc. Soc. Exper. Biol. & Med. **29**: 717. 1932.

The influence of posterior pituitary extract, pitressin, on mineral and water exchange was studied in 2 boys aged 9 and 5 years. The effect of the injected pitressin lasted about 3 hours, during which time there was a retention of water and a large increase in urinary excretion of Na and Cl. After 3 hours there was a marked loss of water, exceeding the storage during the antidiuretic period by several hundred grams. The increased Na and Cl excretion persisted throughout the period of diuresis.—M. O. L.

The sexual hormone of the anterior hypophysis (Ein Beitrag zur Kenntnis des sexualen Hypophysenvorderlappenhormons). Schmidt, A. A. and Elisabeth Derankowa, Ztschr. f. d. ges. exper. Med. **78**: 361. 1931. Abst., Chem. Absts. **26**: 1329.

The female sex hormone of pregnancy urine is quantitatively and irreversibly adsorbed by animal charcoal. One fraction of the hormone from urine is also adsorbed by filter paper, and is released by weakly alkaline phosphate solution. In addition to the hormone, the elutriated material contains a toxic substance which produces convulsions and death in mice. The hypophysis sex hormone of pregnancy urine is quantitatively precipitated by NaCl. The precipitation redissolves in a weakly alkaline solution.

Effect of hypophysectomy on the incisor of the rat. Schour, I. and H. B. Van Dyke, Proc. Soc. Exper. Biol. & Med. **28**: 934. 1931.

A study was made of nine litter-mate controls and 16 completely hypophysectomized rats (145-459 days of post-operative life). The changes in the incisors of the experimental animals were: Retardation and final cessation of eruption; smaller size (⅔ normal); distortion in form; severe histologic alterations.—Authors' Abst.

Effect of replacement therapy on eruption of the incisor of the hypophysectomized rat. Schour, I. and H. B. Van Dyke, Proc. Soc. Exper. Biol. & Med. **29**: 378. 1932.

Following hypophysectomy the eruption of the incisor of the rat becomes progressively slower and finally ceases. If not administered too late after operation, growth-promoting hormone increases the eruption-rate of the incisor. An increase in body-weight, following the administration of hormone to the hypophysectomized animal, is always associated with an increase in the rate of the eruption of the incisor. In the normal animal, the administration of growth-promoting hormone under the experimental conditions described, although definitely increasing body-weight, does not appreciably alter the eruption-rate of the incisor.—Authors' Summary.

The first appearance in the anterior pituitary of the developing pig foetus of detectable amounts of the hormones stimulating ovarian maturity and general body growth. Smith, P. E. and C. Dortzbach, Anat. Rec. **43**: 277. 1931.

The anterior hypophyses of pig foetuses of various ages have been implanted into immature mice in order to determine at which stage of development detectable amounts of the gonadal-stimulating hormone are formed. Similar implants have been made into hypophysectomized rats to determine when the hormone stimulating general body growth is first present. The gonadal-stimulating hormone does not appear in the pituitary in amounts sufficient to be detected by the test until foetuses have reached a crown-rump length of 17 to 18 cm. It is present in amounts sufficient to give a constant maturity effect with moderate dosages only after the 20-to-21-cm. stage. The hormone stimulating general body growth is present in the pituitaries of foetuses 9 to 11 cm. in length, although apparently not in as large amounts as it is at the 11-to-13-cm. stage. Implantation of pituitaries from foetuses 7 to 9 cm. in length gave no growth response. The difference in the time of appearance of these two principles in foetal development shows that they are separate hormons. The stage of development at which detectable amounts of the gonadal-stimulating hormone appear precedes slightly the stage at which Bascom and Osterud found that rapid growth of the testes begins in this form. The formation of this hormone is probably a factor which causes the testes to begin more rapid growth. The stage of development at which the hormone stimulating general body growth is detectable by the test is the same as that at which the hormone of the thyroid appears, as shown by metamorphosis tests with tadpoles by Rumph and Smith. This is not surprising, because of the interrelationship of these glands in general body growth.—Authors' Summary.

The effect of hypophysectomy upon the involution of the thymus in the rat. Smith, P. E., Anat. Rec. **47**: 119. 1930.

The thymi of hypophysectomized rats have been compared as regards weights and structure with those of controls and reference controls. The thymi of rats cease to grow immediately after the ablation of the hypophysis, and regress in weight. In the long survivals the thymi weigh less than one-half those of the controls—a difference, however, which is not shown by percentage weights on body weights, due to difference in the rate of general body growth in the two types of animals. Structurally, the involution of the thymi in the hypophysectomized rats is usually, though not invariably, more advanced than in the controls.—Author's Summary.

The differential effect of hereditary mouse dwarfism on the anterior-pituitary hormones. Smith, P. E. and E. C. MacDowell, Anat. Rec. **50**: 85. 1931.

The reproductive system of dwarf mice, especially in males, is further developed than in hypophysectomized rats, whereas other disabilities are similar in the two types. This suggested that the pituitary growth hormone in the dwarf might be suppressed without a corresponding suppression of the gonad-stimulating hormone. Biological tests for the presence (or absence) of these two hormones show that such is the case. There is a high concentration of the gonad-stimulating hormone in the pituitaries of dwarfs as revealed by implants, whereas the growth hormone is not present in a sufficient amount to have been detected even with the sensitive test form used. These findings are correlated with the disabilities exhibited by the dwarfs.—Authors' Summary.

Biological and chemical studies of extracts of the anterior lobe pituitary. Spaul, A. W. and W. W. Myddleton, J. Exper. Biol. **8**: 30. 1931. Abst., Biol. Absts. **6**: 1635.

A buff colored precipitate is obtained by the addition of N/20 iodine solution to dilute acetic acid extracts of fresh anterior lobe substance. Similar acetic acid extracts of tissues and extracts of the anterior lobe prepared with other extracting media do not give the same precipitate with iodine. The precipitate indicates the presence and gives an approximate measure of the metamorphic factor in fresh gland extracts of the anterior lobe. Dilute acetic acid extracts of the precipitates after removal of the iodine with alcohol are biologically active and characterized by their phosphate content. Similar extracts of the posterior lobe give an iodine precipitate but the phosphate content is much lower than that of the anterior lobe precipitate. The iodine in these precipitates is adsorbed or loosely combined. The biological activity of anterior lobe extracts varies with the time of extraction and the concentration of the extracts. Its resistance to temperature, acid and alkali have been investigated. The metamorphic factor is slowly destroyed by pepsin and rapidly by trypsin.

The phosphate content and the biological activity of the anterior lobe pituitary. Spaul, E. A. and W. W. Myddleton, J. Exper. Biol. **8**: 44. 1931. Abst., Biol. Absts. **6**: 1635.

There is a direct quantitative relationship between the phosphate P precipitated by iodine solution from active extracts of the anterior pituitary lobe in dilute acetic acid and the metamorphic activity of the lobe. Substitution of the phosphate content of the iodine precipitate by other radicles results in the loss of activity. The active factor is insoluble in alcohol, chloroform and ether, which distinguishes it from Robertson's Tethelin. The melanophore stimulant is independent of the phosphate content. There is a small quantity of phosphate precipitated by iodine solution from posterior lobe extracts.

Rôle of pituitary in etiology of cancer. Susman, W., Brit. M. J. **2**: 794. 1931.

A histological survey of the ductless glands of several hundred patients who had died from a variety of conditions showed that in malignant disease (30 cases) the anterior pituitary was more active; this was gauged by the large proportion of acidophilic cells present. Twenty-one showed pronounced sclerosis of the posterior pituitary; nine showed both sclerosis and abundant pigment present; and three much pigmentation. The appearance indicated that the functional capacity in the posterior pituitaries of these cases was much reduced. The pancreas was examined in 14 cases of malignant disease and in all but 2 were the islets enlarged and more numerous. These histological findings on cancer cases lead to the development of the hypothesis that the anterior pituitary was stimulated in cancer cases; that the normal function of the posterior pituitary was to produce a secretion to check growth and this was inadequate in cancer cases because of sclerosis, etc., of that section of the gland; and that the tumor demanded a great deal of carbohydrate. On applying these principles experimentally it was found (a) that application of shale oil to mice induced tumors to form sooner when the animals were fed on abundant carbohydrate and (b) that injections of pituitrin (P. D. & Co.) caused uniform retrogression of the tumors in all animals. The theory was applied therapeutically in human cases. The patients were placed on a diet moderately low in carbohydrates—Pituitrin (P. D. & Co.) 0.5 to 2 cc. once or twice a day was injected subcutaneously to check the growth promoting hormone, and Theelin (P. D. & Co.) 0.25 to 0.5 cc. was given subcutaneously once a day to check the anterior pituitary activity. All 7 cases treated showed definite retrogression in the tumors. A case of early epithelioma included in the group of 7 cases, lost the growing edge to the tumor in 5 days: the tumor began to separate in 14 days, and was enucleated after 7 weeks' treatment.

—W. Susman.

Histogenesis of the hypophysis (Zur Histogenese der Hypophyse). Zimmermann, A., Ztschr. f. mikr.-anat. Forsch. **26**: 216. 1931.

As a result of studying the histological changes in the hypophysis of cattle fetuses from 8 weeks to 9 months of age, it is concluded that histologic differentiation of the pituitary occurs in the early months in intra-uterine life.

During the second half of the fetal period the gland attains a structure which differs very little from the fully developed hypophysis. Chromophilic cells appear during the third month.—A. T. R.

Effect of liver poisoning on the action of parathyroid extract. Greenberg, D. M., Proc. Soc. Exper. Biol. & Med. **29**: 721. 1932.

The author suggests that the liver may be involved in the mechanism of action of the parathyroid hormone. A typical experiment is reported on a dog with the liver damaged by phosphorus. Injection of 100 units of parathormone failed to cause any increase in blood calcium, as compared with a marked response to the same dosage before the liver was poisoned.—M. O. L.

Irradiation of the parathyroids in cystic disease of the bones. Merritt, E. A., J. A. M. A. **98**: 1733. 1932.

Cystic disease of the bones associated with hyperparathyroidism can be successfully treated by roentgen rays as evidenced by the report of a case, the only one of which so treated has been found in the literature. The patient, one year after a subtotal thyroidectomy, developed cystic changes in the lower end of the right femur and a recurrence of symptoms of hyperthyroidism. Following six x-ray treatments of 5 ma. 135 K.V., 10 inch distances, 6 minutes' time, through 5 mm. of aluminum filter, over a period of four months, there was scarcely a trace remaining of the original bone lesion or symptoms of hyperthyroidism.—C. James.

Glycosuria in pregnancy. Chase, Lillian A., Canad. M. A. J. **26**: 279. 1932.

In 100 analyses of the urine of 18 patients, 66 showed sugar, generally less than 1%; the largest amount was 2%. All specimens were taken in the afternoon. Only two of the 18 failed to show sugar at any test. An intelligent patient co-operated by carrying out 100 tests, 4 times a day for 25 days. Of the 100, 47 were positive; sugar was shown most frequently in afternoon specimens, only once in a morning sample. Glycosuria in pregnancy is normal; its frequency depends upon how thoroughly it is sought. It does not predispose to diabetes, and can be differentiated from that by the small quantity of sugar present, the absence of thirst, and the presence of normal blood sugar curves.—A. T. C.

The effect of insulin upon the blood-sugar picture during ether anesthesia (Über den Einfluss des Insulins auf den Blutzuckerspiegel während der Äthernarkose). Eschweiler, H., Arch. f. exper. Path. u. Pharmakol. **161**: 21. 1931. Abst., Chem. Absts. **26**: 1338.

During deep ether anesthesia rabbits develop a significant increase in blood sugar, probably due to a mobilization of sugar from the liver. If insulin is given ½ hour before beginning anesthesia, there is a marked initial insulin hyperglycemia, followed by the usual fall in blood sugar. The inhibition of the anesthesia hyperglucemia is probably due to the fact that the insulin facilitates the building up of glycogen in the liver.

The daily glycosuric curve in various forms of diabetes (Le courbe glycosurique journalière dans les diverses formes de diabète). Faelli, C., Rev. franç. d'endocrinol. **8**: 340. 1930.

Diabetics may be arranged into two groups, (1) in which glycosuria increases after dinner, (2) in which it decreases after dinner. The former is considered the more dangerous type. The determination of these curves permits the differentiation of sympathotonic diabetes from a vagotonic diabetes, a matter of importance in treatment.—B. C.

Some unusual manifestations of the insulin reaction. Feigenbaum, J., Canad. M. A. J. **26**: 410. 1932.

A diabetic patient, aged 21, exhibited some unusual neuropsychiatric manifestations of an insulin reaction, characterized especially by drowsiness and clonic convulsions and persisting after intravenous glucose administration.

Clinical and experimental evidence is put forward to indicate that the nervous system is primarily involved in the symptomatology of an insulin reaction. An insulin reaction is not always accompanied by hypoglycaemia and it does not always respond favorably at once to the administration of glucose.
—A. T. C.

The effect of insulin on growth, nitrogen excretion and respiratory metabolism. Goldblatt, M. W. and R. W. B. Ellis, Biochem. J. **25**: 221. 1931.

Litters of white rats, kept on restricted or unrestricted amounts of food, showed no difference in rate of growth from that of litter mates, when injected with daily doses of insulin varying from 2 to 50 units. Insulin was found to have no effect on the nitrogen excretion in the urine of rats consuming an exclusively fatty diet or during starvation. This was the case whether hypoglycaemia did or did not occur; convulsions were absent. Insulin hypoglycaemia in a starving human subject is associated with a marked increase in R.Q. and hence presumably an increased carbohydrate- and diminished fat-oxidation. This effect passes over as the blood-sugar recovers. Progressive fall in blood-sugar and disappearance of glycosuria may be induced in a glycosuric patient without any change in R.Q. or calorie output. It is considered that this must indicate glycogen synthesis in the liver. Insulin can increase the liver-glycogen of young dogs during starvation without any change in muscle-glycogen. This effect may be accompanied by profound hypoglycaemia. The attainment of blood-sugar values of vanishing proportions may be accompanied by an acute fall in R.Q. It is considered improbable that this fall indicates a true change in metabolism.—Authors' Summary.

Pregnancy glycosuria and pre-natal care. Harding, V. J. and D. L. Selby, Canad. M. A. J. **26**: 283. 1932.

The author's experience indicates that the incidence of glycosuria in pregnancy is high and may well be 100% in small series of cases. Study of numerous cases leads to the following differential diagnosis pointing to physiological glycosuria rather than to diabetes. Absence of history and symptoms of diabetes (although thirst, polyuria and pruritis vulvae have been reported as accompanying physiological pregnancy glycosuria and might be expected in a few cases in which there is continuous high output of sugar due to a very low renal threshold); absence of sugar in the fasting urine unless that be very concentrated; absence of ketonuria.—A. T. C.

The present status of the high carbohydrate-low calorie diets for the treatment of diabetes. Rabinowitch, I. M., Canad. M. A. J. **26**: 141. 1932.

Of over 500 diabetics placed on a high carbohydrate-low calorie diet only 16 failed to respond satisfactorily and of these 3 did not respond to the older diets. In as yet some unknown manner, it is stated, exposure to this diet appears to lead to an increase in the available supply of insulin. The view held generally at present is that, in diabetes, there is defective production of insulin. Many of the author's experimental data to date fail to support this view. Diabetes does not appear to be due to defective production of insulin but to interference with the action of a normal supply.—A. T. C.

The influence of infection upon the reaction of the diabetic to insulin treatment; report of an unusual case. Rabinowitch, I. M., Canad. M. A. J. **26**: 551. 1932.

A male, 64 years of age, with a history of diabetes of 3 years' duration, and with the disease complicated by cardio-vascular-renal disease and prostatic enlargement with cystitis and pyuria, was admitted to hospital in pre-coma. Following the usual treatment of the coma condition he was placed on high carbohydrate-low fat diet, and some three weeks later was exposed to a cystotomy and 11 days later to enucleation of the prostate. After subsequent recovery and before the patient left hospital, it was possible to discontinue insulin entirely, although the diet had a carbohydrate content of over 200 grams.
—A. T. C.

Preparation of thyroglobulin. Barnes, B. O., Proc. Soc. Exper. Biol. & Med. **29**: 680. 1932.

A new rapid method of preparing thyroglobulin is described which involves extracting fresh thyroids with sodium acetate and precipitating the thyroglobulin at the isoelectric point with acetic acid. If a soluble preparation is desired, the precipitate coming down within 1-2 hours is centrifuged and dissolved in sodium acetate plus enough sodium hydroxide to maintain neutrality. —Author's Abst.

Studies on the velocity of blood flow: the circulation in myxedema with a comparison of the velocity of blood flow in myxedema and thyrotoxicosis. Blumgart, H. L., S. L. Gargill and D. R. Gilligan, J. Clin. Investigation, **9**: 91. 1930.

Sixteen series of measurements were made in 7 patients with myxedema in order to correlate the clinical manifestations with changes in the velocity of blood flow, basal metabolic rate, pulse rate, plasma volume, venous and arterial pressures, respiratory minute volume and vital capacity of the lungs. In each patient measurements when the basal metabolic rate was low were compared with subsequent measurements when the basal mtabolic rate had been elevated to normal by appropriate doses of thyroid gland by mouth. The plasma volume per kilogram of body weight was low and tended to increase on administration of thyroid gland. The vital capacity of the lungs was strikingly diminished in all subjects in the absence of any signs of congestive heart failure and did not show significant change following treatment. The extent of diminution in the vital capacity was not closely related to the degree of lowering in the basal metabolic rate. The velocity of blood flow was strikingly slow in every subject and corresponded closely with the degree to which the metabolic rate was lowered. After taking thyroid gland by mouth, the rise in the metabolic rate and the increase in the velocity of blood flow to normal took place simultaneously and closely paralleled each other. The great increase in velocity of blood flow and consequent increased cardiac work that occurs when the basal metabolic rate is raised to normal affords a rational explanation of the clinical manifestations of cardiac insufficiency which occur not infrequently following thyroid gland therapy in myxedema. The changes in the pulse rate, basal metabolic rate and velocity of blood flow in myxedema are compared to those previously reported in thyrotoxicosis. The comparison indicates that the increased velocity of blood flow in thyrotoxicosis is due to the increased basal metabolic rate rather than to a specific toxic effect on the heart. The findings emphasize the close interrelation between blood flow and metabolism and throw additional light on the degree, manner, and results of changes in the circulation associated with increased and decreased metabolic rates.—Authors' Abst.

Studies on rat thyroids. Drennan, A. M., J. Malcolm and G. A. Cox, Brit. J Exper. Path. **12**: 430. 1931. Abst., Chem. Absts. **26**: 1644.

Attempts were made to produce a diet adequate for normal growth in the rat, but sufficiently low in iodine to produce thyroid change. This was best achieved by a diet of white bread and fresh milk. After a period, rats on this diet developed an active type of gland, low in iodine content, and large relative to the body weight. The addition of small quantities of iodine to such a diet kept the thyroids small, and with a rich iodine content. When iodine was again omitted from the diet the thyroids tended to enlarge and assume the active type of gland similar to those that had no iodine from the beginning.

Geographic location and the iodine content of the thyroid gland. Fenger, F., R. H. Andrew and J. J. Vollertsen, J. Am. Chem. Soc. **53**: 237. 1931. Abst., Biol. Absts. **6**: 1630.

Calculated on the desiccated fat-free basis, the yearly average for hog thyroid glands from North Dakota is 0.32% iodine, while that of Texas glands is 0.60% iodine. The seasonal variation in the iodine content is most pronounced in the northern glands. The higher iodine level of the Texas glands and the greater seasonal fluctuations of the North Dakota thyroids are attributed to the geographic location of the two states.

Use of potassium iodide in hyperthyroidism. Frazier, C. H., Ann. Surg. **95**: 517. 1932. Abst., J. A. M. A. **99**: 76.

The author reports a series of cases of both forms of toxic goiter (hyperplastic toxic goiter and toxic adenoma), which were prepared for operation with potassium iodide. The general improvement noted, as well as the specific improvement in pulse and metabolic rate, paralleled the improvement obtaind by compound solution of iodine. The clinical charts of several representative cases are exhibited which graphically show the preoperative response of thyrotoxicosis to potassium iodide. The author concludes from the evidence obtained in a surgical research laboratory that free iodine, to be absorbed, must be converted into an iodide, and from his clinical investigation, that it appears unnecessary to have free iodine "loosely combined," to which quality has been ascribed the effect of the administration of compound solution of iodine on hyperthyroidism.

Lymphatic system of the thyroid gland. Gordon, S. D., Canad. M. A. J. **25**: 46. 1931.

Experimental injections of India ink into the thyroid lymphatics of dogs indicated that the capsular and interglandular lymphatics of the thyroid communicate freely with one another. The capsular system drains into the superior, inferior and pre-tracheal lymph nodes. There is no evidence (as was suggested by Williamson and Pearse's work) that there is a second closed system draining into the thymus.—A. T. C.

Thyroid crisis. Greene, E. I. and J. M. Greene, Ann. Surg. **95**: 537. 1932. Abst., J. A. M. A. **99**: 76.

According to the authors, thyroid crisis is one of the most serious complications of hyperthyroidism. As a rule this condition occurs in the primary toxic, or exophthalmic, goiter. Thyroid crisis usually occurs in patients known to have hyperthyroidism but in whom no treatment has been sought or in whom inadequate treatment has been instituted. It may occur in individuals in whom there is no suspicion of thyrotoxicosis. A crisis may come on immediately after operation or several days later. Acute hyperthyroidism may be ushered in by physical fatigue, by psychic stimulation or as a result of an intercurrent infection, or may appear after some surgical condition often trivial. Measures not aimed to relieve the hyperthyroidism should be postponed until after thyroidectomy has been performed. Adequate preoperative therapy will in the majority of cases prevent postoperative acute thyroidism. The picture of crisis may appear suddenly with no premonitory manifestations, or make its appearance slowly with definite symptoms. The mechanism whereby a crisis is set into motion is not known. The condition must be recognized early and proper therapy instituted immediately or death will frequently result. Treatment consists of iodine, fluids, dextrose and morphine. After recovery from a crisis, surgical intervention should be done with caution and after one has waited long enough to get the patient in proper physical condition.

The treatment of obesity. A comparison of the effects of diet and of thyroid extract. Lyon, D. M. and D. M. Dunlop, Quart. J. Med. **1**: 331. 1932. Abst., Physiol. Absts. **17**: 283.

All of 35 subjects lost weight while dieting, the rate of weight loss being inversely proportional to the caloric value of the diet. The rate was greatest at first and decreased as the diet was continued. With an intake of 1,000 calories per diem, the loss was greatest when the carbohydrate was kept low. It is stated that nine grains of thyroid extract produced the same loss of weight as the standard 1,000 calories diet; the loss was proportional to the dose given. The basal metabolic rate was normal on admission; it fell during undernutrition and rose 20 points when thyroid was given. On a low diet the loss of weight is due to loss of fat and water; when thyroid is given, the loss due to water is a greater fraction of the whole and some protein may also be lost.

The differential diagnosis for "borderline" cases of hyperthyroidism. McGregor, J. K., Canad. M. A. J. **25**: 152. 1931.

A case is described exhibiting a persistently high basal metabolic rate without corresponding degree of loss of weight, a high rapid pulse uninfluenced by Lugol's solution, lack of heat intolerance, cold hands, absence of tremor, and no apparent abnormality of the thyroid itself. At subsequent post-mortem the thyroid was found to be normal; no thymus was found; while in the right renal space there was an encapsulated tumor of the adrenal about 6 cm. in diameter, which examination showed to be a carcinoma of the malignant type of adenoma described by Ewing.—A. T. C.

Spontaneous rupture of the thyroid gland. McGregor, J. K. and W. G. Cornett, Canad. M. A. J. **26**: 711. 1932.

A case is reported which is considered unusual in that a spontaneous hemorrhage originating in an adenomatous cyst ruptured completely through the thyroid capsule, infiltrated the muscle and fascial planes of the neck, spread into the mediastinum, and was of sufficient severity to cause death.—A. T. C.

The thyroid factor in family periodic paralysis. Morrison, S. and M. Levy, Arch. Neurol. & Psychiat. **28**: 386. 1932.

A case is presented of a man of 24 in whom exophthalmic goiter and periodic attacks of paralysis coexisted. Following partial thyroidectomy the symptoms of the exophthalmus were partially alleviated as was true also of the paralysis attacks. The case is cited as further evidence that the condition of familial periodic paralysis is due in part at least to endocrine factors. It is suggested that these may be operative merely by lowering the general health to a sufficient extent to render the patient overtly vulnerable to the specific etiologic factor—whatever that may be.—R. G. H.

Thyroxine and the central nervous system (Thyroxine und Zentralnervensystem). Schittenhelm, A. and B. Eisler, Klin. Wchnschr. **11**: 9. 1932. Abst., Physiol. Absts. **17**: 207.

Rabbits, cats, and dogs were used. Injection of 1 mgm. per kgm. thyroxine causes an increase in the iodine content of the midbrain and tuber cinereum, most marked after 4 hours, and returning to normal in 3 days. Other parts of the brain or spinal cord do not show this response to thyroxine. Hypo- or athyreosis in animals produces a diminution of iodine in the mid-brain and tuber cinereum, but not in other regions of the brain. The authors suggest that their results indicate an interrelation between internal secretions and definite parts of the central nervous system.

A survey on goiters in North America (A contribution to their knowledge in general and to their etiological and evolutive determination) (Estudio sobre bocios en el norte argentino [contribución a sue conocimiento en general y al de su determinismo etio-fisiopatoginico y evolutivo]). Sola, E., Sexta Reunion de la Sociedad de Patologia Regional del Norte Argentina, **1**: 876. 1931.

A study is reported of 2000 patients definitely showing goiter. The types varied, some being simple and some toxic. In some families the two types alternated with corresponding shift in the nervous systems. Among the etiological factors recognized were lack of iodine, treponena infection, food and avitaminosis. Potassium iodide as a prophylactic failed in considerable proportion of the cases. Ninety-nine per cent of the patients showed dental caries. This is regarded as a co-existent result of the cause of the goiter rather than due to the goiter itself, though in many patients arrest of the caries was followed by arrest of the goiter. No correlation could be seen between an instance of goiter and acquired syphilis but a high correlation was observed with hereditary lues. To the co-existing lues is ascribed the "goiter heart" seen in some cases. Goitrous foetuses showed a high incidence of hepatic and splenic enlargement. Toxic goiter with exophthalmos was never seen in the aboriginal patients studied.—Condensed from Author's Abst.—R. G. H.

Study of thyroid activity in normal pregnancy. Soule, S. D., Am. J. Obst. & Gynec. **23**: 165. 1932.

Anselmino and Hoffman have demonstrated that a substance fulfilling all the prerequisites for thyroxine is present in increased concentration in the blood stream of pregnant women. Our experiments involved the injection of pregnancy serum into male mice and the determination of mouse liver glycogen. The results demonstrated that a substance which lowered the level of liver glycogen is present in the pregnancy serum in greater concentration than in the non-pregnant state. This substance parallels the action of thyroxine and the pregnant woman may be considered to be in a physiological state of hyperfunction of the thyroid gland.—Author's Abst.